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THE PREPARATION AND CLINICAL ADMINISTRATION OF LYOPHILIZED PLATELET MATERIAL TO CHILDREN WITH ACUTE LEUKEMIA AND APLASTIC ANEMIA

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HEMOSTASIS has been observed following the clinical administration of platelet concentrates which had been stored at subzero temperatures.[1] This suggested that the morphological integrity of platelets may not be essential for the retention of at least some of the in vivo functions of intact platelets. The storage and availability of platelet material would be considerably simplified if the various platelet functions were resistant to lyophilization. In vitro studies indicated that thromboplastin-generating activity,[2] antifibrinolysin activity,[3] accelerating activities in the clotting of recalcified plasma,[2, 4] and antiheparin activity[5] were at least partially retained by platelet material after lyophilization. It has also been established that the lyophilized platelet material (LPM) does not excessively activate coagulation in vitro.[2, 4]

Lyophilized platelet material was therefore investigated in vivo and was found to be free of toxic or thromboembolic sequelae in animals.* This report presents preliminary studies in relation to the clinical administration of this material and its effects on the coagulation status in secondary thrombocytopenia.

METHODS AND MATERIALS

Preparation of Lyophilized Platelet Material.—Platelet concentrates were prepared by the methods described previously.[1, 6] In order to simplify the process,[6] the unit shown in Fig. 1 was used for the preparation of about 100 platelet concentrates. Under sterile conditions 20 c.c. of Solution A† is

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†Solution A contains 150 parts of ACD solution (NIH formula) and 20 parts of a 2 per cent solution of Triton No. WR 1339 (Rohm and Haas Co., Philadelphia, Pa.) per liter of 0.85 per cent saline.

drawn into the plastic transfer bag* containing the packed platelet concentrate in approximately 15 c.c. of residual plasma. The platelets are suspended and the mixture is centrifuged (2,500 r.p.m.—International Centrifuge, Model PR 2) for thirty minutes. The supernatant is removed at 4° C. for twenty-four hours to permit vasoconstrictors of small molecular weight to diffuse into the supernatant.[7] Another 20 c.c. of Solution A is added to the packed platelets; the platelets are resuspended and the suspension is kept at 4° C. for another twenty-four hours. The supernatant is

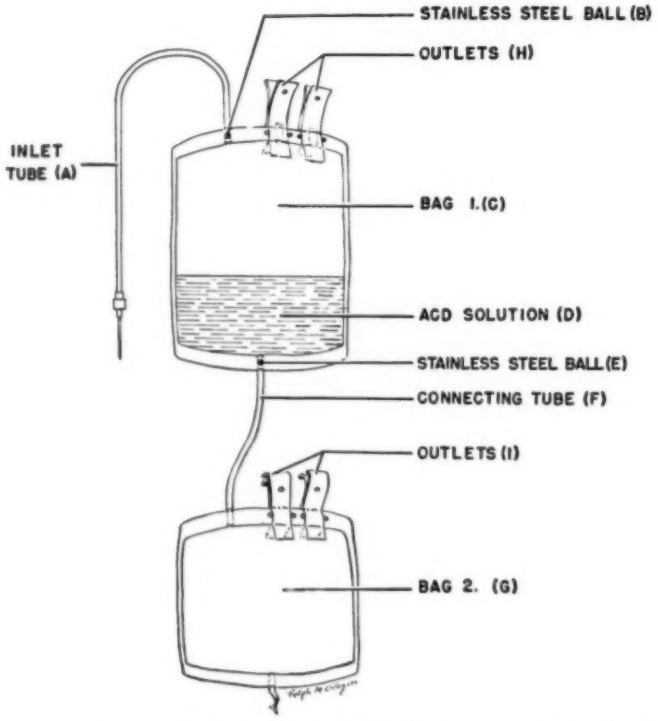

Fig. 1.—Closed system of two plastic bags for the separation of blood components.† Preparation of platelet concentrates according to methods previously described,[1, 5] with the following modifications. (1) Clamp connecting tube (*F*). (2) After blood has been collected, invert bag No. 1 (*C*) and place in centrifuge cup with connecting tube (*F*) pointing upward. (3) Dislodge steel ball (*E*) from connecting tubing (replace clamp beyond point to which blood has penetrated, if necessary). (4) Centrifuge at 500 g for twenty minutes. (5) Transfer platelet-rich plasma to bag No. 2 (*G*). (6) Centrifuge at 1,800 g for forty-five minutes. (7) Return plasma to bag No. 1, leaving 15 c.c. of plasma with platelet concentrate.

and 20 c.e. of Solution A is added again to the packed platelets which are resuspended. This suspension is kept

*Fenwal Laboratories, Inc., Framingham, Mass.

†This unit was designed with the cooperation of R. T. Earl, Technical Service Manager, Fenwal Laboratories, Inc., Framingham, Mass.

removed after centrifugation as before. The packed platelets are now suspended in Solution B.* The suspension is transferred to a 60 c.e. vial, shell-

*Solution B contains 150 parts of ACD solution (NIH formula) and 20 parts of a 2 per cent solution of Triton No. WR 1339 per liter of distilled water.

frozen, and lyophilized. After lyophilization has been completed, the vial is filled with superdry nitrogen and sealed.

Administration.—The dry platelet material is resuspended, in 20 c.c. of physiological saline or a solution of 5 per cent glucose in water, prior to intravenous administration through a plastic recipient set with nylon filter. Following the infusion of platelet material, 50 c.c. of the suspending solution is administered to clear the transfusion set.

The selection of recipients was limited to children between the ages of 2 and 17 years, with platelet counts of less than 10,000 per cubic millimeter. The patients were in the late stages of leukemia (seven patients), other malignancies (two patients), and aplastic anemia (one patient). The patients were bleeding and had failed to respond to the usual measures for the control of hemorrhage (whole blood transfusions, vitamins, and topical application of hemostatic agents).

Method of Evaluation of Effects.—The coagulation status was examined before, and within twelve hours after, the infusion of lyophilized platelet material. The following tests were carried out to exclude coagulation deficiencies unrelated to thrombocytopenia: Lee and White clotting time, recalcification time, one-stage prothrombin time, thromboplastin generation test, and prothrombin consumption. Only those patients were included in this series whose coagulation deficiencies were referable entirely to thrombocytopenia and were corrected by platelets in vitro. All patients in this group had a prothrombin consumption of 30 per cent or less prior to administration of LPM.

Of sixty-four infusions of LPM only ten infusions were given without prior administration of frozen or fresh platelet concentrates. In order to limit observations to the possible effects of LPM, only those hemorrhagic episodes are included here in which it alone was given.

Control of hemorrhage was assessed according to the following criteria: (1) Directly observable bleeding (such as epistaxis) ceased within thirty minutes and did not recur for at least six hours; (2) occult bleeding (hematuria or melena) ceased within twenty-four hours and did not recur for forty-eight hours. Specific observations of the hemorrhagic state were timed from the termination of the administration of LPM. The same criteria were applied to an analogous group of patients who had received banked whole blood. Specific observation of the hemorrhagic state began when the transfusion was completed.

RESULTS

One-hundred-eighty units* of LPM were administered to ten thrombocytopenic patients in sixty-four infusions. The amount of LPM varied from two to five units per first infusion. The largest quantity given at one time was ten units to a 4-year-old boy. The largest total number given to a single patient was forty-five units, over a period of fourteen days. The maximum rate of administration was 2 units q.4.h. for seventy-two hours.

The relevant changes in the coagulation status of the patients are reflected by the prothrombin consumption before and after administration

*One unit is the amount of platelet material obtained from one pint of blood, averaging approximately 400 mg.

of LPM. The results are summarized in Table I.

TABLE I. PROTHROMBIN CONSUMPTION TWELVE HOURS AFTER ADMINISTRATION OF LYOPHILIZED PLATELET MATERIAL

NO. OF TESTS	CORRECTED*	PARTIALLY† CORRECTED	NOT CORRECTED
29	24	4	1

*Corrected to 100 per cent.
†Corrected by at least 50 per cent.

The patient whose prothrombin consumption had remained uncorrected received a second infusion of 10 units of LPM within twenty-four hours, whereupon the prothrombin consumption was corrected by 100 per cent.

The data on hemostasis following the infusion of dried platelet materials are shown in Table II.

TABLE II. HEMORRHAGIC STATUS FOLLOWING INFUSION OF LYOPHILIZED PLATELET MATERIAL OR BANKED WHOLE BLOOD

INTRAVENOUS MEDICATION	NUMBER OF PATIENTS	HEMOSTASIS	HEMORRHAGE NOT CONTROLLED
Lyophilized platelet material	10	5	5
Banked whole blood	10	1	9

There were no significant changes in the platelet counts after infusion of LPM. Overt bleeding was arrested in three patients within five to ten minutes after the administration of dried platelet material. Occult bleeding disappeared in three patients within twelve to twenty-four hours.

Bleeding remained arrested in three patients on continued administration of dried platelet concentrates. Bleeding started again in two patients on continued, but perhaps quantitatively inadequate, administration of dried platelet material. Bleeding continued after the administration of dried platelet material, again in possibly inadequate amounts, in five patients. In an analogous group of ten patients, to whom platelet concentrates could not be administered, temporary hemostasis occurred in one patient.

Side effects of the intravenous injection of LPM are venospasm and pain at the time and site of infusion. A mild, transient elevation of the blood pressure has occurred on two occasions. Thromboembolic phenomena have not been observed clinically following the administration of LPM. At post-mortem examination (seven cases) no evidence of thrombosis or embolism was found.

DISCUSSION

This investigation was undertaken in preparation of more extensive clinical trials. The caution required in this initial study of the clinical administration of LPM may have resulted in the administration of suboptimal doses. The lack of clinical experience with LPM did not permit correlation of dose and rate of administration with the age, weight, or the clinical or hematological status of the patient. Since there are no methods for quantitating platelet requirements in terms of the severity of bleeding, the level of prothrombin consumption was arbitrarily selected as a guide for estimating platelet requirements.

Hemoglobin values and transfusion requirements do not adequately reflect platelet requirement or efficacy. The level of circulating hemoglobin is affected by such factors as changes in blood volume and the balance between production and destruction of red cells, in addition to direct blood loss.

These additional factors are of considerable importance in the advanced stages of malignant disease and are difficult to quantitate.

It also appears that prothrombin consumption is not an adequate indicator of platelet requirements. Correction of prothrombin consumption is not necessarily accompanied by hemostasis. The amounts of LPM required for the correction of defective prothrombin consumption varied considerably in different patients in analogous clinical states and in the same patient at different times.

The corrective effect of LPM on the defective prothrombin consumption suggests that this agent may provide a means for specific substitution therapy in the respective types of thrombasthenia.

The relatively small number of patients in this series precludes definitive conclusions in regard to the hemostatic efficacy of LPM. Our data do not indicate how long the effects of LPM are maintained in vivo. Hemostasis may be maintained, although the prothrombin consumption has already returned to the defective preinfusion state. It appears that the respective rates of utilization or disappearance of the several activities of LPM differ with each hemorrhagic episode. This may be one of the reasons for the differences in platelet requirements and effectiveness.

In two patients, in whom the circulating antifibrinolysin levels were determined, elevations of antifibrinolytic activity were observed following LPM administration.[3] This is of interest, since the presence of antifibrinolytic activity in platelets has been previously demonstrated in vitro.[8]

The level of circulating platelets was not elevated following infusions of LPM. It therefore appears that morphologically intact platelets are not required for at least some platelet activities.

Evidence for hypersensitization has not been obtained. Two of the patients in this group, whose bone marrow improved eventually due to therapy for the underlying disease, showed normal thrombocytogenesis.

The effects of the in vitro addition of LPM to platelet-depleted normal plasma and thrombocytopenic plasma on the coagulation mechanism have been reported elsewhere.[2, 4] High concentrations of LPM (approximately ten times the equivalent of physiological concentrations) inhibit various phases of the coagulation mechanism, while the equivalent of physiological levels corrects the coagulation defects of platelet-poor plasma. Coagulation is not promoted excessively at any concentration of platelet material. Thus the in vitro activities of LPM do not constitute a contraindication against the administration of high concentrations of dried platelet material. According to these findings the hypothetical hazard of thrombosis at the site of infusion would be reduced because the concentration of platelet material would be highest at that site, predisposing toward hypocoagulability. Upon dilution of the platelet material within the recipient's circulation, normal coagulation rates would be approached. This has been borne out by observations on rabbits and Chinese hamsters in which toxic effects or excessive in vivo coagulation have not been encountered following the administration of homologous or human LPM.

Thromboembolic sequelae to the intravenous administration of LPM have not been encountered in this group of patients. In a more extensive group which has been investigated recently, LPM has been equally harmless.[11] The clinical impression of the lack of thromboembolic phenomena and toxicity has been substantiated by postmortem studies in about 80 per cent of the total series. These findings suggest the safety of LPM.

One of the practical advantages of LPM is that it can be freed considerably of vasoconstrictor agents which may complicate, by severe discomfort and venospasm, the administration of fresh or frozen platelet material.

LPM retains a number of the in vitro activities of platelets, such as antiheparin activity,[5, 9, 10] antifibrinolysin activity,[3, 8] and thromboplastin-generating activity.[2, 12] There are a number of specific pathological processes in which LPM might be of clinical use in providing the respective activity.

LPM has been kept in sealed vials at room temperature for twelve months or more without indication of loss of activities. It therefore can be stored and transported without elaborate precautions.

SUMMARY

Lyophilized platelet material has been administered intravenously to patients with secondary thrombocytopenia without toxic or thromboembolic sequelae. Defective prothrombin consumption has been corrected by this platelet preparation, but its effects on hemostasis, although suggestive, require further investigation. The safety and stability of this material indicate the possibility of making various platelet factors, such as the antifibrinolysin, antiheparin, and thromboplastin-generating activity, readily available.

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UNEXPECTED DEATH IN EARLY LIFE

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FORTUNATELY, instances of sudden, unexpected death occurring in previously healthy infants and children or in those with apparently only mild illnesses are uncommon in the experience of most physicians. When such tragedies do occur every effort must be made to determine the exact cause of death. Not only must death from criminal causes be excluded but also, whenever possible, the family must be made to understand that they were in no manner responsible for the death of their child.

An adequate explanation of such deaths can be obtained only by complete post-mortem examination, clinical observations usually being too brief to warrant any conclusions. Both the clinician and the pathologist performing the necropsy should be cognizant of the types of lesions which may be responsible for sudden death in early life, and even their combined efforts may fail to demonstrate an adequate cause of death in a relatively small percentage of such infants and children.[1] In the majority of instances, however, an adequate cause of death will be demonstrated by complete post-mortem studies, including histologic, bacteriologic, and chemical studies, combined with clinical observations whenever these are available.

During the six-year period, 1949 to 1954 inclusive, there were 95,195 new admissions to the outpatient department of St. Christopher's Hospital for Children, and 18,366 infants and children were admitted to the hospital. Thirty-three patients were dead at the time of arrival, ten died in the outpatient department and seventy-one died within twenty-four hours after admission to the hospital. This represents a mortality of 1.0 per 1,000 total admissions. The over-all mortality for patients admitted to the hospital during this same period was 17.9 per 1,000. Autopsies were performed on 103 of these 114 patients (90 per cent); this represents 31 per cent of all autopsies conducted by the hospital during this period of time.

Seventy-six of the 114 patients died during the first year of life. The greatest frequency was during the first two months of life, this period accounting for thirty-five of the 114 deaths. Eighteen patients were between 1 and 2 years of age, and only twenty were older than 2 years. Eighty-five deaths occurred during the months September through April and twenty-nine occurred during the four remaining months. Males and females were approximately equally represented. Seventy-eight patients were

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white and thirty-six were Negro; this racial distribution is comparable to that of the general admissions to the hospital.

Before any discussion of the various lesions encountered at post-mortem examination of these patients is begun, certain differences between this material and that commonly reported in the literature as "sudden death" in infants and children should be noted. For the most part the present series consists of infants and children in whom clinical manifestations of illness were present for a variable but usually short period of time prior to death, but in whom for various reasons the severity of the illness was not appreciated. Moreover, all patients dying within twenty-four hours after admission to the hospital are included, regardless of the presence or absence of previous hospital admissions. Therefore, in approximately one-third of the 103 patients upon whom autopsies were performed a well-recognized pre-existing disease, often of a serious nature, was known to have been present for some time prior to death. The present material is thus not entirely comparable with that often reported as "sudden death" in previously healthy infants and children and, instead, is more indicative of the disease processes responsible for death following brief and apparently mild illnesses.

The causes of death among the 103 patients upon whom post-mortem examinations were performed are listed in Table I. As with most reported series of unexpected deaths, infections were the leading cause of death,[2-6] accounting for forty-two of the 103 deaths. These are tabulated in Table II.

Table I. Causes of Death

Infections	42
Congenital malformations	18
Miscellaneous	25
Undetermined	18
Total	103

Table II. Infections as a Cause of Death

Septicemia	16
Bronchopneumonia	6
Leptomeningitis	6
Acute epiglottitis, laryngotracheitis or tracheobronchitis	3
Ecthyma gangrenosum	3
Miscellaneous	8
Total	42

Eleven of the sixteen patients in whom septicemia was considered to be the primary cause of death were infants 6 months or less of age, one of whom died during the neonatal period. Only two patients in this group were over 2 years of age. One child, aged 2 years 9 months, in whom symptoms had been apparent for only two days, died as a result of staphylococcal pyemia secondary to an acute osteomyelitis of the fibula; multiple abscesses were present in the heart, kidneys, and lungs.

In three patients death was attributed to the presence of bilateral adrenal hemorrhages associated with purpura (Waterhouse-Friderichsen syndrome) (Fig. 1). The infants were 5, 11, and 20 months of age. In one of these infants symptoms were of twenty-four hours' duration; in the remaining two, mild symptoms were present for several days, followed by a severe illness of six and one-half and twenty-four hours, respectively. Histologic evidence of meningitis, although minimal, was present in all these infants; in one it was confined to the spinal leptomeninges; the meningitis was not recognized macroscopically. *Neisseria*

meningitidi microorganisms were isolated from the blood, cerebrospinal fluid, and nasopharynx of one infant during life, but cultures of the blood and cerebrospinal fluid obtained post mortem were sterile. An atypical meningococcus was isolated from the blood stream of one infant, but blood cultures in the third infant revealed no growth. Nevertheless, because of the clinical and pathologic findings these last two infants are included in this group.

Fig. 1.—Bilateral adrenal hemorrhage. The responsible organism was not identified either during life or at the time of autopsy.

The mechanism responsible for death in patients with the Waterhouse-Friderichsen syndrome is unknown. Conflicting evidence regarding the role of adrenal insufficiency has appeared, and only rarely have low levels of 17-hydroxycorticosteroids in the blood been reported.[7-9] That a comparable clinical picture may occur in the absence of massive adrenal hemorrhage has been demonstrated by Rich,[10] who described degenerative changes in the adrenal cortex in association with severe acute infections.

Blood cultures obtained either during life, immediately post mortem, or at the time of autopsy grew pneumococci in eight instances and beta hemolytic streptococci in four. In five of these patients the positive blood culture was the only significant finding, no apparent portal of entry being demonstrable at autopsy. In the remaining seven patients, however, the positive blood culture was associated with other evidences of infection which were demonstrable at

necropsy; in two patients there was an associated dermatitis and in one patient each there were pneumonia, necrotizing bronchiolitis, bilateral otitis media, acute omphalitis, and pneumococcal peritonitis associated with lipoid nephrosis.

In the entire series of 103 patients there were ten in whom death may be considered as having occurred suddenly and unexpectedly in a previously healthy infant. The ages of these ten patients varied from 5 weeks to 4 months. In four of these, death was attributed to pneumococcal septicemia, in two, to beta hemolytic streptococcal septicemia, and in four no cause of death was demonstrated (Table III). In one of these infants dying with septicemia a mild serotal dermatitis was present, another had bilateral otitis media, and in the remaining four no significant findings were present other than the positive blood culture.

TABLE III. CAUSES OF SUDDEN, UNEXPECTED DEATHS IN PREVIOUSLY HEALTHY INFANTS

Pneumococcal septicemia	4
Beta hemolytic streptococcal septicemia	2
Undetermined	4
Total	10

The significance of positive blood cultures obtained during the agonal period or after death is difficult to evaluate, and the importance of even pathogenic organisms in post-mortem blood cultures is questioned by some investigators.[3] In general, however, positive blood cultures of pneumococci, beta hemolytic streptococci, meningococci, or *Hemophilus influenzae* are obtained at post-mortem examination only from patients in whom other evidences of infection are apparent, or those in whom death occurs unexpectedly and in whom no other cause of death is apparent after a complete post-mortem examination. The presence of gram-negative bacilli *(Pseudomonas aeruginosa, Proteus vulgaris, and Escherichia coli)* or enterococci in agonal or post-mortem blood cultures is usually of little or no significance; occasionally, however, when an apparent portal of entry is present, such as ulcerative lesions in the colon and skin associated with ecthyma gangrenosum, their presence in the blood stream may be indicative of an actual septicemia. Staphylococci are usually considered as contaminants unless associated with obvious evidences of infection produced by these organisms, e.g., metastatic abscesses.

The varied significance of different types of organisms in the blood agonally or after death is not entirely clear. It seems possible, however, that the facility with which different organisms may invade the blood stream at this time may be as dependent upon their location and numbers within the body as upon intrinsic differences in the bacteria themselves. Thus, the normal inhabitants of the gastrointestinal tract, usually present in large numbers, are rather commonly present in the blood stream after death, but their presence is usually of little or no significance. Other organisms, such as pneumococci, beta hemolytic streptococci, and *H. influenzae*, do not usually attain sufficient numbers in the body to be demonstrated in post-mortem cultures unless an associated infection produced by them is also apparent, or unless they occur as part of an overwhelming infection in infants dying suddenly and unexpectedly.

The mechanism responsible for death in this group of patients is certainly not clear. In certain instances the septicemia was merely a part of clearly demonstrable infectious processes within the body, e.g., pneumococcal peritonitis or leptomeningitis. In one instance the septicemia was present in association with a widespread pneumonic process and the clinical manifestations were predominantly those of severe diarrhea with associated hyperelectrolytemia; in this patient the metabolic disturbances may well have been the major factor responsible for death. In still other instances, however, the septicemia was present in association with relatively localized infectious processes, such as otitis media, or no demonstrable localized infection was present. In such instances, when organisms commonly considered as pathogenic are isolated from the blood stream, death is arbitrarily attributed to septicemia, but it must be recognized that this is only an arbitrary and admittedly unsatisfactory explanation of death. Bacteremia per se is probably of relatively frequent occurrence, and many patients with septicemia recover or die only after manifesting signs and symptoms of an infection for some time. In the present group of patients, however, evidences of severe illness were present for twenty-four hours or less in thirteen of the sixteen patients, and in six of these death occurred suddenly and unexpectedly. Since bacteremia cannot be differentiated from septicemia by isolated cultures of the blood, and since the usual clinical manifestations of sepsis were not apparent, it is obviously impossible to prove that death actually was caused by septicemia. It seems highly probable that their deaths are in some way related to infection, but the exact mechanism must, for the present, remain unexplained. Perhaps an inability to respond to infection, associated with diminished levels of gamma globulin,[11] may be important, but preliminary studies in our laboratory have failed to demonstrate any apparent relationship between the levels of gamma globulin demonstrable in blood obtained at autopsy and the occurrence of sudden, unexpected death. Further work concerning this aspect of the problem is certainly indicated and is currently being conducted.

In six patients death was attributed to bronchopneumonia. In no instance was the presence of only a few neutrophils in the alveoli considered adequate to explain the death of an infant or child; all six patients had histologic evidence of a moderate to severe acute inflammatory process in the pulmonary alveoli. Their ages varied from 16 hours to 2½ years; two were less than 1 month of age. In one patient each the pneumonia was associated with congenital heart disease and otitis media, bilateral otitis media and acute tonsillitis, bilateral otitis media, fetal anoxia, acute omphalitis, and with thromboses of the dural sinuses with infarction of the brain; in the last patient death may well have occurred as a result of the cerebral changes, but the pneumonia was believed to have antedated the infarction of the brain.

In two of the patients in whom death was attributed to pneumonia death occurred after an acute, severe illness of apparently only a few hours' duration. Although mild symptoms were present for some time in several patients, in only one did the acute,

severe illness exceed twenty-four hours in duration.

Leptomeningitis was responsible for the death of six patients, whose ages ranged from 3 weeks to 2½ years. In one infant 22 days old the meningitis was caused by *Proteus morganii* and was secondary to a myelomeningocele. In the remaining patients the responsible organisms were *H. influenzae* in two, and *Mycobacterium tuberculosis,* pneumococci, and coliform organisms in one each. The duration of symptoms in these patients varied from one and one-half days to one week.

Three patients died as a result of acute infections of the epiglottis, larynx and/or trachea and bronchi. Their ages varied from 9 months to 4 years; only one was less than 2 years of age. Cultures of the involved areas yielded *H. influenzae* in one, *H. influenzae* and pneumococci in one, and *Staphylococcus aureus* in one. Mild symptoms were present from one to three days in all of the patients, but the severe illness was as short as two hours prior to the death of one child in whom there was occlusive swelling of the epiglottis and aryepiglottic folds.

Ecthyma gangrenosum was considered responsible for the death of three infants whose ages ranged from 2 weeks to 8 months. Diarrhea lasting from one to several weeks had been present in two and possibly in the third infant; in all there were ulcerative lesions of the scrotum and of the perineum or buttocks. *Ps. aeruginosa* microorganisms were obtained in cultures from the stool of one infant. In the other two, cultures of the blood at the time of post-mortem examination were positive for the same organism. In one infant there were multiple large punched-out ulcers distributed throughout the colon (Fig. 2); in another only a mild acute enterocolitis was noted histologically. In the third infant, 2 months of age, the

Fig. 2.—Multiple ulcers of colon. *Pseudomonas aeruginosa, Streptococcus faecalis,* and coliform organisms were isolated from these lesions. Diarrhea had been present for several weeks.

lymphoid aggregates of the small and large intestine were devoid of lymphocytes and were replaced by a neutrophilic exudate. There was in addition a remarkable paucity of lymphocytes in the mesenteric lymph nodes and in the Malpighian corpuscles of the spleen. These findings are similar to those described in a child with "alymphocytosis,"[12] and are suggestive of those associated with agammaglobulinemia.[13, 14] Unfortunately, electrophoretic studies were not available to prove or disprove this diagnosis. In none of the other patients in the entire series were comparable evidences

of lymphocytic depletion present to suggest this diagnosis on a morphologic basis.

Death was attributed to acute enteritis in two infants 3 and 5 months of age, respectively. Diarrhea of two to five days' duration had been noted clinically. This was associated with dehydration and, in one infant, with severe acidosis. *Pr. vulgaris* and coliform organisms were isolated from the stools of both infants. Histologically, increased numbers of myeloid cells and neutrophils were present in the lamina propria of the small bowel and the mesenteric lymph nodes contained increased numbers of neutrophils. Certainly the causative relationship between the organisms isolated from the stools, the inflammatory changes in the bowel, and the diarrhea noted clinically cannot be established. Bronchiolitis and emphysema, with an infiltrate of lymphocytes in the walls of the bronchioles, were present in both infants and suggest the possibility that a viral agent might have been responsible for both the pulmonary and intestinal lesions; again, however, proof of this is lacking. In one infant the inflammatory infiltrate in the walls of the bronchioles also involved the interalveolar septa, and neutrophils were present within a number of alveoli; in this infant the possibility of a parenteral diarrhea secondary to bronchopneumonia cannot be excluded. In any event, death probably occurred as a result of metabolic disturbances secondary to diarrhea. The inclusion of these infants among those who died as a result of an infectious process appears to be justified, and they are rather arbitrarily considered as examples of acute enteritis of undetermined etiology.

Isolated examples of staphylococcal pulmonary abscess, interstitial myocarditis, rheumatic carditis, postinfectious (measles) encephalitis, chronic aspiration pneumonia, and chronic interstitial pneumonia were also included in the group of patients dying as the result of infections. The chronic aspiration pneumonia occurred in a Negro female infant 2½ years old with microcephaly, congenital panhypopituitarism, and congenital heart disease, who had had symptoms referable to the congenital malformations since birth. She had been hospitalized on several occasions prior to her final admission, at which time she was dead at the time of arrival. The chronic interstitial pneumonia occurred in association with an organizing pneumonia in a small, premature infant 1 month of age who had been hospitalized elsewhere since birth; she died while being transferred to St. Christopher's Hospital for Children.

The interstitial myocarditis occurred in an infant 7½ months of age in whom mild symptoms had been present for about two days, but who died shortly after admission to the hospital. At necropsy the heart was enlarged and there was endocardial sclerosis confined to the left atrium. Histologically there was severe edema of the interstitial tissue of the myocardium, with focal and diffuse infiltrates of lymphocytes. The importance of examining multiple sections of the myocardium in order to demonstrate the presence of "isolated myocarditis" has been emphasized by others and was well exemplified here, since the inflammatory infiltrate was entirely absent in some of the sections prepared.

CONGENITAL MALFORMATIONS

The types of congenital malformations encountered are listed in Table IV. Among the patients with congenital heart disease, exclusive of the instances of endocardial sclerosis, the ages ranged from 12 days to 6 years, only four patients being older than 6 months. For one patient no record of the presence or absence of preexisting cardiac disease was available. In two patients no cardiac disease had been recognized prior to the terminal illness, but the remaining ten patients were known to have congenital cardiac malformations. Two patients with mongolism are included in this group of congenital malformations; a third child with mongolism and congenital heart disease (Eisenmenger's complex) died as a result of severe bronchopneumonia and a fourth as a result of postinfectious encephalitis; these last two are therefore included in the group dying as a result of infections.

TABLE IV. CONGENITAL MALFORMATIONS

Tetralogy of Fallot	2
Transposition of great vessels with interventricular septal defect	2
Endocardial sclerosis	2
Endocardial sclerosis with coaretation of aorta	1
Atrioventricularis communis with patent ostium secundum	1
Atrioventricularis communis with pulmonary stenosis	1
Atrioventricularis communis with anomalous pulmonary venous return	1
Anomalous pulmonary venous return (partial) with pulmonary hypertension	1
Transposition with overriding pulmonary artery (Taussig-Bing)	1
Cor biloculare with pulmonary atresia	1
Cor triloculare biatrium with rudimentary left ventricular outflow chamber	1
Interventricular septal defect with patent ductus arteriosus	1
Interventricular septal defect (with coarctation?)	1
Hydranencephaly	1
Diaphragmatic hernia	1
Total	18

No attempt will be made to discuss all of the congenital malformations of the heart encountered. The two infants with simple interventricular septal defects, however, deserve special mention. In one infant 6 months of age this was associated with a widely patent ductus arteriosus. In the second infant, 5 months of age, there was questionable coaretation of the aorta in addition to a low interventricular septal defect. The possibility that the so-called "coaretation" of the aorta represented only the normal physiologic narrowing which is commonly encountered in small infants in the descending aorta between the left subclavian artery and the ductus arteriosus could not be excluded. In both instances the heart was over twice its normal size, and severe pulmonary congestion was present histologically. In the first infant increased pulmonary blood flow may have resulted from the left-to-right shunt brought about both by the widely patent ductus arteriosus and by the interventricular septal defect. In the second infant the explanation of the cardiac hypertrophy and pulmonary congestion is not as apparent. The possibility that these were largely the result of the narrowing of the aorta could not be excluded but seemed unlikely because of the minor degree of this narrowing. Although mild bronchopneumonia and right otitis media

were also present in this infant, the findings indicated that death occurred as a result of left-sided cardiac failure. In both infants, then, the observations suggest that interventricular septal defects, especially if associated with other lesions which might enhance the pressure in the left ventricle or might increase pulmonary blood flow, may not be the innocuous lesions that they are commonly considered to be, and may even be lethal in early infancy.

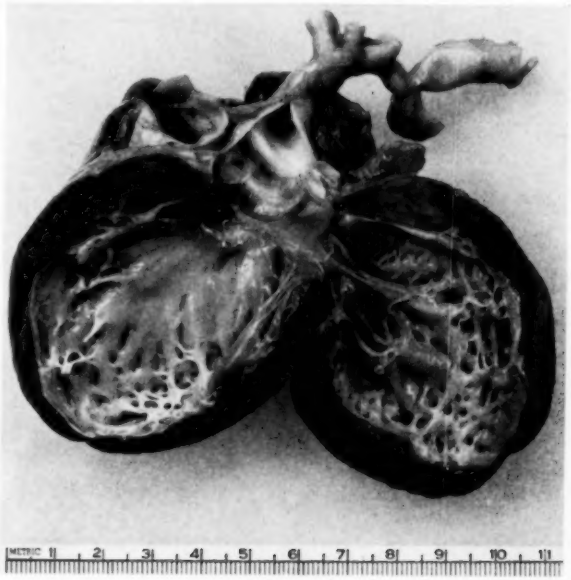

Fig. 3.—Endocardial sclerosis in an infant 6½ months of age. Note the hypertrophy of the myocardium of the left ventricle, the thick, opaque mural endocardium and the prominent columnae carneae at the apex. The aorta is narrowed at the level of the entrance of the ductus arteriosus.

Endocardial sclerosis was responsible for the death of three infants, all between 6 and 7 months of age. The duration of symptoms in one patient, in whom there was an associated coaretation of the aorta is not recorded; symptoms were of only two days' duration in the remaining two infants. The clinical manifestations were quite nonspecific, i.e., lassitude, irritability, fever, cough, dyspnea, and cyanosis. Prior to demonstration of the enlarged heart by physical or roentgenologic examination these symptoms were usually attributed to a respiratory infection. At post-mortem examination there was severe cardiac enlargement, with thickening and opacity of the mural endocardium and increased prominence of the columnae carneae at the apex of the left ventricle (Fig. 3). The valvular endocardium was not involved and the changes were predominantly in the left side of the heart.

In one patient death was attributed to hydranencephaly, the cerebral hemispheres being virtually absent and the lateral ventricles covered by a thin, delicate membrane. A diagnosis of cytomegalic inclusion disease had been made within a few days

after the birth of this infant, the characteristic inclusion bodies being present in the urine and subsequently in fluid obtained by "subdural" (probably ventricular) puncture. Death occurred at the age of 1 year. No inclusion bodies were noted in the remnants of the brain at necropsy, but they were present in the salivary glands, kidney, pylorus, and thyroid.

One infant died at 1 day of age as a result of a left diaphragmatic hernia. A superficial tentorial tear, minimal bronchopneumonia, and "hypoplasia" of the left lung were also noted at autopsy.

MISCELLANEOUS CAUSES OF DEATH

The miscellaneous causes of death are listed in Table V.

TABLE V. MISCELLANEOUS CAUSES OF DEATH

Intestinal obstruction and/or perforation	6
Poisoning	5
Fibrocystic disease of the pancreas	2
Pulmonary hyaline membranes	2
Malignant lymphoma	2
Acute glomerulonephritis	1
Chronic glomerulonephritis	1
Diabetes mellitus	1
Renal tubular necrosis, severe	1
Aplastic anemia with cerebral hemorrhage	1
Galactosemia	1
Erythroblastosis fetalis	1
Fetal anoxia (580 gram premature infant)	1
Total	25

Six patients died as a result of intestinal obstruction and/or perforation. Their ages ranged from 6½ weeks to 6 years, and only one was more than 2 years of age. Clinical manifestations had been present for one and one-half to six days in all of the patients; in only one was there any known pre-existing disease (anaphylactoid purpura). The types of lesions encountered are listed in Table VI.

Certainly intestinal obstruction or perforation cannot be considered as a cause of unexpected death occurring without premonitory symptoms. However, the severity of the illness may not be appreciated by the parents or physician, and death may occur as a result of perforation with peritonitis or imbalance of fluids and electrolytes. The present group of patients further emphasizes the importance of early recognition and treatment of such conditions.

Five patients died as a result of poisoning. The youngest infant, 35 days old, had had boric acid packs applied to the buttocks because of the presence of excoriation of the skin of the scrotum and buttocks, presumably the result of diarrhea. When first seen he was in extremis, dying while still in the outpatient department. He was severely dehydrated, the buttocks were wasted, and there was severe excoriation of the skin of the buttocks and scrotum, the latter appearing fiery red. Caked masses of boric acid were present over the buttocks and scrotum. Post-mortem examination revealed histologic evidence of acute enteritis, with an exudate of neutrophils in the glands at the base of the lamina propria of the small intestine; there was a questionable increase of myeloid cells in the lamina propria of the small intestine but no evidence of acute inflammation of the mesenteric lymph nodes. A number of the acinar cells of the pancreas

TABLE VI. INTESTINAL OBSTRUCTION AND/OR PERFORATION

Intussusception	2
Volvulus	1
Mesenteric hernia	1
Acute appendicitis with perforation	1
Perforation of rectosigmoid (glass?)	1
Total	6

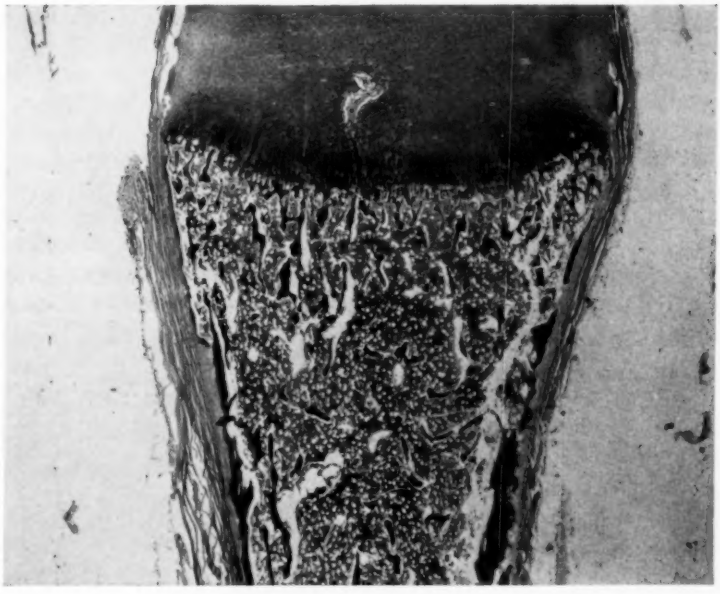

Fig. 4.—Costochondral junction from a child 3 years of age with no evidence of lead poisoning. The normal metaphyseal zone should be compared with that present in Fig 5. (×15; reduced ¼.)

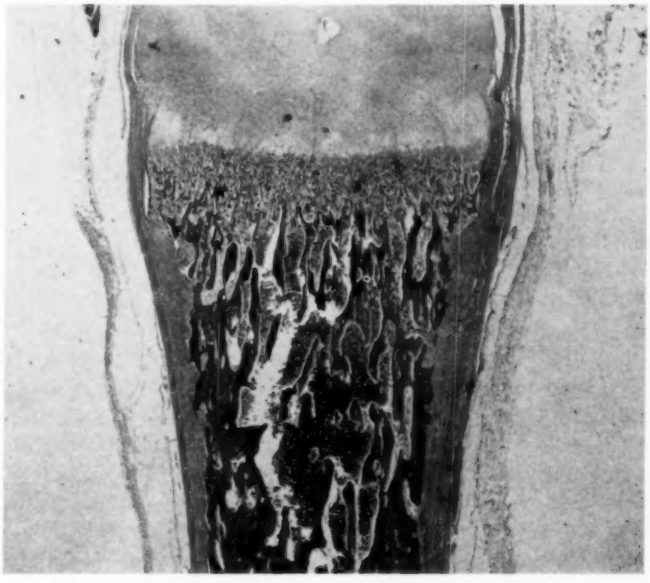

Fig. 5.—Costochondral junction from a child 2 years of age with lead poisoning. Note the broad zone of closely packed, persistent cartilaginous trabeculae in the metaphysis. It is this zone which is responsible for the dense radiopaque line visible in the roentgenograms. (×15; reduced ¼.)

contained discrete cytoplasmic vacuoles, some of which contained spherical blue bodies. Specimens of liver, kidney, and brain were submitted to Dr. Russell S. Fisher, Chief Medical Examiner of the State of Maryland, for determination of their content of boric acid. The results were as follows: kidney: 100.1 mg. per cent as boric acid; liver: 71.0 mg. per cent; brain: 107.0 mg. per cent. The boron equivalents of these were 17.5, 12.4, and 18.7 mg. per cent, respectively, quantities of boron which were believed by Dr. Fisher to be of clinical significance.[15] However, it was his impression that such quantities of boron were somewhat lower than those generally encountered in fatal boric acid poisoning, and that the boric acid poisoning merely served as a contributory factor to the death of the infant. Perhaps the combination of acute enteritis, dehydration, and boric acid poisoning should be considered as responsible for death. The changes in the pancreas are suggestive of those described in patients with boric acid poisoning.[16]

One infant 22 months of age died as a result of severe pulmonary edema and bronchopneumonia approximately three and one-half hours after ingesting lighter fluid.

Three children died as a result of lead encephalopathy. They were 2, 2, and 3 years of age, respectively. Mild symptoms had been present from ten days to two months prior to admission to the hospital; severe symptoms were from fifteen hours' to two and one-half days' duration. Postmortem examination revealed evidence of severe cerebral edema in all, the cerebral convolutions being broad and flat and the sulci shallow. Histologic examination of the costochondral junctions revealed persistence of the calcified cartilaginous trabeculae at the line of ossification.[17] About the trabeculae were considerable numbers of multinucleated giant cells (Figs. 4 and 5). Intranuclear acidophilic inclusion bodies were present in the kidney in all three patients.[18] In one the inclusions stained positively with the Kinyoun stain for acid-fast structures.

The importance of routine histologic examination of the costochondral junctions was emphasized by the observations in these patients dying as a result of lead encephalopathy. In one instance the diagnosis was first suggested because of the abnormal persistence of calcified cartilaginous trabeculae at the line of ossification of the ribs. Subsequently, roentgen films of excised ribs which had been preserved in 10 per cent formalin revealed abnormally wide densities at the costochondral junctions (Fig. 6), and correlation of the clinical record with the macroscopic and histologic findings of the post-mortem examination established the diagnosis beyond reasonable doubt.

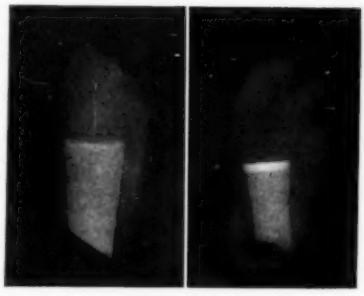

Fig. 6.—Roentgenograms of costochondral junctions after fixation in 10 per cent formalin. The specimen on the left is from a child 3 years of age with no evidence of lead poisoning. That on the right is from a child 3 years of age with lead poisoning. Note the broad radiopaque metaphyseal zone in the latter.

Two patients died as a result of fibrocystic disease of the pancreas. One of these, a newborn infant 18 hours of age, died as a result of meconium peritonitis following perforation of the colon; histologic examination confirmed the diagnosis of fibrocystic disease of the pancreas. The second infant, 6½ months of age, had had mild fever, vomiting, and diarrhea for a period of about four days, followed by evidence of severe dehydration for only five and one-half hours prior to death. No clinical manifestations suggestive of fibrocystic disease of the pancreas had been noted. Post-mortem examination revealed evidence of severe dehydration, but no explanation for this was apparent until histologic preparations of the pancreas were examined. These revealed well-advanced dilatation of the pancreatic acini with "inspissation" of secretion, disappearance of many acini, retention of islets of Langerhans, and increased amounts of interstitial connective tissue (Fig. 7). The lungs were somewhat emphysematous; the changes commonly associated with fibrocystic disease of the pancreas were also apparent in Brunner's glands, the intestinal glands, and in the glands of the trachea and bronchi. Since this infant died during a period of excessive heat in August, it seemed highly probable that death had occurred as a result of the excessive loss of sodium, such as is known to occur in patients with fibrocystic disease of the pancreas.[19, 20]

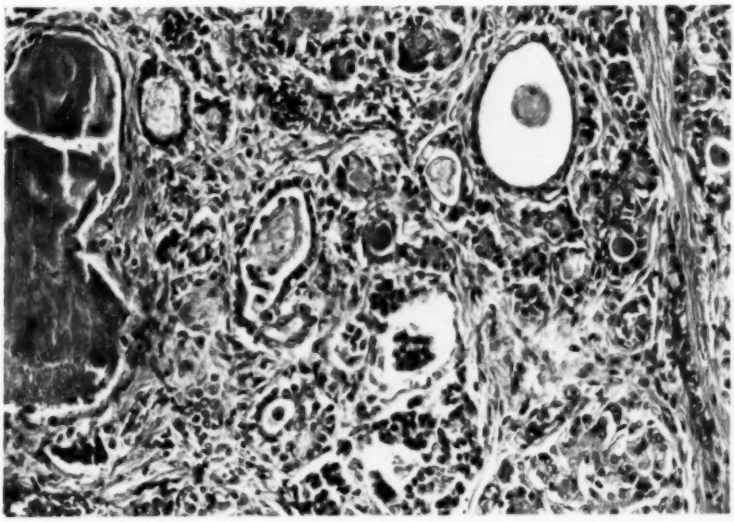

Fig. 7.—Fibrocystic disease of the pancreas. Note the dilated acini filled with secretion and the increase of connective tissue. A portion of a normal island of Langerhans is present in the lower right-hand corner. (×255; reduced ⅓.)

No attempt will be made to discuss the remaining patients, whose deaths were attributed to a variety of causes. However, some mention should be made of the eighteen infants and children (17 per cent) in whom no obvious cause of death was apparent after completion of the post-mortem examination (Table VII). Their ages varied from 24 hours to 3½ years;

TABLE VII. PATIENTS WITH NO ANATOMIC CAUSE OF DEATH

Cerebral damage	6
Bronchopneumonia, mild	2
Interventricular septal defect	1
Chondrodystrophy	1
Bilateral tentorial tears	1
Anemia, severe (abruptio placentae)	1
No significant lesions	6
Total	18

twelve were less than 6 months of age. In four of these patients the death may be considered as sudden, occurring in previously healthy infants.

Five patients in whom no immediate cause of death was apparent were known clinically to have cerebral lesions of some type, as manifested by spastic quadriplegia, hypotonic cerebral palsy, microcephaly, and failure of development. Since the lesions encountered at autopsy in the central nervous systems of these patients appeared to have been of some duration, probably having had their onset at or before birth, these patients are arbitrarily included in the group in whom the cause of death was undetermined. In still a sixth patient included in this group, in whom malnourishment had been a prominent clinical manifestation since shortly after birth, there were bilateral encapsulated subdural hydromas demonstrated at the post-mortem examination. Again, because of the apparent chronicity of these lesions they are not considered as affording an adequate explanation for the death of the infant at the time it occurred. Nevertheless, in all these six patients it must be admitted that death may well have been in some way related to the cerebral damage, even though this had been compatible with existence for a considerable period of time, and the decision to include them in the group of patients in whom no cause of death was demonstrated is a purely arbitrary one.

In two of these six patients mild bronchopneumonia was present but was considered insufficient to be responsible for death. In a third patient there was clinical evidence of dehydration. Thus, it seems probable that infants and children with severe damage to the central nervous system may die as the result of relatively minor illnesses which would not be fatal to an otherwise normal child.

DISCUSSION

Unexpected or unanticipated deaths include: (1) those occurring after a brief and apparently mild illness, and (2) sudden deaths occurring in apparently healthy infants and children. Such an arbitrary division is not always a valid one, however, and is dependent in part upon the accuracy of clinical observations in the period preceding death. The present discussion is concerned primarily with the former group of patients, only ten of the 103 patients actually dying suddenly and unexpectedly while in apparent good health. Septicemia was responsible for six of the ten sudden deaths and for ten of the ninety-three deaths occurring during the course of a recognized illness.

An attempt has been made to include as causes of death only those lesions which might be accepted by the majority of pathologists, and to abstain from attributing death to lesions of doubtful significance. Thus, although mild or questionable degrees of cellular infiltrates were occasionally encountered in the interalveolar septa in these patients, they were not

accepted as an adequate anatomical cause of death. Comparable changes may be found in infants dying of a variety of causes, and may also be observed in some surgically removed specimens of lung. Such morphologic changes have been attributed to a viral infection[21, 22] but, with few exceptions, careful attempts to isolate a virus have been unsuccessful.[6, 23] Furthermore, evaluation of the presence or absence of slight thickening and mild inflammatory infiltration of the interalveolar septa is often difficult in small infants because of approximation of adjoining alveolar septa and because of the relatively wide septa normally present in the lungs of young infants, especially those born prematurely. As a result, the diagnosis of mild interstitial pneumonitis has often been an equivocal one and does not appear to explain the deaths of these infants on an anatomical basis. Such a diagnosis has often been used to indicate the presence of an overwhelming infection,[24, 25] but in the absence of positive cultures of bacteria from the blood stream the presence of a mild interstitial pneumonitis does not appear sufficient to substantiate the occurrence of an overwhelming septicemia.

There is no intent to deny the occurrence of inflammatory processes wholly or in large part confined to the interstitial tissue of the lung. The occurrence of such lesions in association with atypical pneumonia, pertussis, plasma cell pneumonia, and the like, is too well recognized to necessitate further mention. However, the lesions usually described as interstitial pneumonia in infants dying suddenly are hardly comparable to these more generally accepted entities, and do not appear to be an adequate cause of death.

Aspirated gastric contents, e.g., curdled milk, are commonly encountered in the trachea of infants dying of a variety of causes. In the absence of other findings death is often attributed to suffocation secondary to aspiration of vomitus. In the presence of some well-recognized disease process, however, such aspiration is usually considered only as an incidental, inconsequential finding. In either event, it seems more logical to consider the aspiration of vomitus as an agonal occurrence and not as a primary cause of death. Massive aspiration of gastric contents should not occur in otherwise healthy infants with intact cough reflexes, and in the absence of definite evidence of obstruction, as by a bolus of food lodged in the larynx, death should not be attributed to this cause.

Much has been written concerning the occurrence of accidental suffocation by bedclothes as a cause of death in apparently healthy infants, but no substantial evidence of the occurrence of such a process is available.[26] The diagnosis of suffocation should not be made simply because an infant is found dead face down in bed, nor is such a diagnosis justified merely because significant lesions are absent at the time of autopsy. Complete postmortem examinations, including bacteriologic studies, will reveal infections as the cause of most such deaths, but in some no adequate cause of death can be demonstrated. In the absence of an unequivocal history of suffocation, e.g., homicidal suffocation or accidental strangulation by hanging, such deaths should not be attrib-

uted to suffocation and the family should be made to understand that they were in no way responsible for the death of their child. The pathologist can perform a real service to the family by establishing the actual cause of death, and by his refusal to incriminate the family on inadequate evidence.

Failure to recognize the rapidity with which thymic involution may occur in association with a variety of illnesses has led to an erroneous conception of the size of the normal thymus in infants and children. Since the majority of deaths in early life are preceded by an illness of at least a few days' duration, a normal (or relatively large) thymus is the exception rather than the rule in any routine post-mortem series. Moreover, the relatively large size of the lymph nodes and lymphoid aggregates usually encountered at autopsies in children is not generally appreciated. As a result, the concomitant occurrence of prominent lymph nodes and lymphoid aggregates and an "enlarged" thymus in infants and children dying suddenly while in apparent good health, or following anesthesia, minimal infections, or other trivial causes, has led to the theory of lymphatism or status thymicolymphaticus. These so-called thymic deaths have been attributed to a variety of vague and unproved causes, including suffocation by tracheal compression, anaphylaxis, the liberation of "thymic lymph toxin" and adrenal insufficiency. That some such deaths may result from adrenal insufficiency has been neither proved nor disproved, but there is no conclusive evidence that the thymus per se is in any way responsible for these deaths, and the term "status thymicolymphaticus" might better be omitted from medical writings.

SUMMARY

An adequate cause of death has been demonstrated in eighty-five of 103 infants and children who either were dead at the time of arrival in the hospital or died within twenty-four hours after admission; only ten in the entire group can be considered as sudden, unexpected deaths occurring in previously healthy infants.

Infections were the leading cause of death, being responsible for forty-two of the 103 deaths; minor infections, such as otitis media or minimal pneumonic processes, were not considered an adequate explanation of the death of an infant or child. The importance of obtaining post-mortem cultures of the blood of infants who die suddenly and unexpectedly is emphasized, and the significance of the presence of different types of microorganisms in post-mortem cultures of the blood is discussed.

Congenital malformations, involving especially the heart, were responsible for eighteen of the 103 deaths. In over one-half of these patients the presence of a congenital malformation had been recognized for some time prior to death.

Mild cellular infiltrates in the interalveolar septa were not included as a cause of death, nor was aspiration of gastric contents into the trachea. There was no evidence that any of the infants died as a result of suffocation. It is suggested that the term "status thymicolymphaticus" might better be omitted from medical writings.

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MECONIUM STAINING OF NEWBORN INFANTS

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MECONIUM staining of the amniotic fluid is one of the classic signs of fetal distress in utero. Eastman[1] states that fetal distress may be suspected when the amniotic fluid presents a yellow-green appearance and contains meconium. He writes that the presence of meconium-stained amniotic fluid is not in itself an indication for delivery but demands close watching of the fetal heart rate. He concludes that this sign is without significance in breech presentation, since it may be caused by mechanical pressure on the fetal abdomen.

Since 1945 Clifford[2] has been interested in the infant stained with yellow vernix. He believes that these infants have suffered a prolonged exposure to meconium which has been passed into the amniotic sac. He concludes that this phenomenon follows fetal anoxia secondary to placental dysfunction. In his experience, the presence of yellow nails and vernix staining has been associated with a higher neonatal morbidity and perinatal mortality. This work has been confirmed by Taylor and co-workers[3] in Scotland. Recently, Walker[4] in Aberdeen published a series of figures in which he correlated the per cent saturation of oxygen in the umbilical vein at delivery with the recent passage of meconium by the infant. He found that a level of oxygen saturation of 30 per cent or less was associated with the passage of meconium. He concludes that at this level, "the distress level," the infant does not obtain enough oxygen to survive indefinitely in utero. It is possible that meconium may be passed in utero by a twofold mechanism following anoxia. Van Liere[5] reports the initial effect of hypoxia on the small bowel to be one of hyperperistalsis, soon followed by ileus. In the late stages of anoxia a relaxation of the sphincter ani occurs concomitant with shock and flaccidity.[1]

In spite of the potential seriousness of meconium-stained amniotic fluid at delivery, the recent literature contains few references to its incidence. In 1925 Schultze[6] found it occurred in 3 per cent of all deliveries. In a review of the signs of fetal distress, McCall and Fulsher[7] in 1953 reported an incidence of 0.5 per cent. Recently White[8] from Australia reported an over-all incidence of 5 per cent.

Since meconium staining of the amniotic fluid is so frequently associated with the delivery of vigorous infants, it alone is not universally considered to be an absolute sign of fetal distress. This is emphasized by the

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finding that hospital labor and delivery records frequently carry no description of the character of the amniotic fluid. The relationship between meconium discoloration of the amniotic fluid at birth and difficulties encountered in the infant born of such a delivery has not been clearly established. If meconium is indeed present in amniotic fluid as a result of antenatal hypoxia, it would be of great value to know if an association exists between the presence of such fluid and some of the difficulties encountered during the neonatal period as well as later in life, such as cerebral palsy, epilepsy, behavior disorders, and mental deficiency. Since December, 1953, a coordinated study of this problem has been conducted in this institution by the departments of obstetrics, pediatrics, and pathology. Infants born of mothers whose deliveries are complicated by the presence of meconium-stained amniotic fluid have been observed in the nursery for evidence of neonatal difficulty and for evidence of meconium staining of the skin and nails.

The present report is concerned with the incidence of meconium-stained amniotic fluid at delivery, and the characteristic appearance of the infants exposed to such fluid, together with a consideration of the involved pigments. A study of the prenatal and natal factors associated with its production is in progress.

SUBJECTS

All patients were seen as inpatients on the obstetrical service of Jefferson Davis City-County Hospital over a thirteen-month period (Dec. 1, 1953, through Jan. 1, 1955, inclusive). Patients here come from the lowest income group in the community. Seventy-four per cent are Negro and 26 per cent white (largely Latin-American). A large percentage (44 per cent) have had no prenatal care. The average patient stay is forty-eight hours for primiparas and twenty-four hours for multiparas.

The color of the amniotic fluid, membranes, cord, and placenta were noted and recorded by the physician attending the delivery. Only deliveries associated with the birth of liveborn infants were considered in this study. After the infants were admitted to the nursery, they were examined by a pediatric resident physician. An attempt was made to note the presence or absence of staining of the infant's body. During the last six months of the study period these infants were placed briefly under a Wood's ultraviolet light as part of the initial physical examination.

The delivery immediately subsequent to the one associated with meconium-stained amniotic fluid was utilized as a control delivery.

INCIDENCE

Amniotic fluid, described as yellow, green-yellow, or meconium stained, was found to be present at delivery in 407 of 3,865 consecutive deliveries, an incidence of 10.9 per cent. This figure is high compared to those of Schultze in 1925 (3 per cent) and McCall and Fulsher in 1953 (0.5 per cent). It is twice that recently reported by White in Australia (5.0 per cent). When the cases of blood incompatibility (nine), high intestinal obstruction (three), and breech delivery (thirteen) are eliminated from the total, the incidence is 9.6 per cent.

The majority (96.6 per cent) of infants in the meconium-stained amniotic fluid group were of term weight. The percentage of premature deliveries (4.4 per cent) is less than that present in the control series (11.6 per cent).

Of the total 408 infants, fourteen (3.4 per cent) died during the neonatal period. Eight of these were term infants. (One infant weighed less than 1,000 grams and was not included in the total.) In the control group the neonatal mortality was 1.5 per cent, with one term death. An additional seventy-eight infants experienced some difficulties in the immediate neonatal period, as against twenty-five in the control group. A total of fifty-five (13.4 per cent) infants in the meconium-stained amniotic fluid series had apnea neonatorum requiring active resuscitation, while this was required in thirteen (3.2 per cent) of the control series.

THE CHARACTER OF MECONIUM-STAINED AMNIOTIC FLUID

Normal amniotic fluid is a clear or slightly cloudy solution, slightly alkaline in reaction, with a specific gravity of approximately 1.008. It is hypotonic to maternal serum and is composed of 98 per cent water. The remaining 2 per cent is composed of inorganic salts, urea, creatinine, lanugo hair, vernix, and epithelial cells. The average volume at term is 1,500 c.c.

Meconium is a viscid semisolid material composed of 70 to 80 per cent (by dry weight) mucopolysaccharides, desquamated cells, vernix, lanugo hair, and cholesterol.[10] It derives its color from a large amount of bile pigment (biliverdin, bilirubin) excreted by the fetal biliary tract. It is first found in the gastrointestinal tract of the fetus after the fourth or fifth month of gestation. The color is usually described as dark green-brown to black.[9] However, during the course of this study it was noted that, although meconium is usually dark, it may be lighter in color, with a mustard yellow or a tan appearance. On exposure to light and air the color becomes darker, tending toward a uniform green-black. Meconium-stained amniotic fluids range from a green to tan to orange-yellow, according to the color of the parent meconium. On four occasions the infant at delivery was found to be passing yellow meconium which was associated with a similar coloration of the amniotic fluid. Some abnormal fluids were, as noted by Clifford, extremely scant and viscid. The early fluid passed on rupture of the membranes often appeared less viscid than that which followed the delivery of the fetus. It was noted that the white linen draping the patient tended to assume a yellow stain regardless of whether the amniotic fluid was green or yellow in color.

THE DURATION OF EXPOSURE TO MECONIUM-STAINED AMNIOTIC FLUID REQUIRED FOR STAINING OF THE INFANT

If, as it has been postulated by Clifford and Walker, the passage of meconium-stained amniotic fluid is an indication of fetal hypoxia, it then becomes of interest to find how long a time is required for the various parts of the fetus and placenta to show visible staining. This would permit a rough estimation of the length of time before delivery when the oxygen saturation of the fetus becomes low enough to cause the fetus to pass meconium while in utero.

Normal newborn infants less than 24 hours of age and born of deliveries in which the amniotic fluid was noted to be clear were utilized as experimental subjects. The feet were immersed in rubber gloves containing meconium solutions or abnormal amniotic fluids. After exposure for various periods, the feet were washed under running water, the moisture removed with absorbent paper, and the nails checked for yellow staining under natural light. The results are shown in Table I. A minimum of four to six hours is required for staining under these conditions. It may then be concluded that if the nails of the infant show slight yellow staining the time of meconium passage was at least four to six hours prior to delivery. It is difficult to determine this more precisely for any one infant, since there are several variables involved (i.e., the amount of bile pigment present in meconium, the amount of meconium passed, and the amount of amniotic fluid present).

TABLE I. DURATION OF EXPOSURE OF INFANTS' NAILS TO MECONIUM OR MECONIUM-STAINED AMNIOTIC FLUIDS NECESSARY FOR STAINING TO BECOME VISIBLE IN NATURAL AND ULTRAVIOLET LIGHT

	CONCENTRATION	NUMBER OF CASES	TIME REQUIRED FOR MINIMAL YELLOW STAINING OF NAILS	TIME REQUIRED FOR LOSS OF NORMAL NAIL COLOR UNDER UV LIGHT
Normal meconium in saline	1%	4	1½-2 hr.	1 hr.
	5%	4	1-2 hr.	45 min.-1 hr.
	10%	3	45 min.-1 hr.	30 min.-1 hr.
Pooled meconium-stained amniotic fluids	Undiluted	6	4-6 hr.	2-4 hr.

Normal vernix was placed into meconium-stained amniotic fluid and incubated at body temperature. At intervals the vernix was removed by filtration and washed with distilled water. The first definite yellow staining was noted at twelve hours in one instance, and at fourteen hours in another.

These periods correspond with those seen in vivo. In two cases membranes were artificially ruptured to induce labor. In both, the fetal head was ballotted above the inlet to permit free escape of fluid. At the time of amniotomy, the amniotic fluids were clear. In one instance the infant was delivered four and one-half hours after amniotomy. Staining of the nails was present but not of the vernix and cord. In the second instance, the infant was delivered fourteen hours after amniotomy. This infant showed yellow staining of the vernix as well as of the cord and the nails. The conditions under which these infants were born are not strictly comparable to the usual conditions, since the time of intrauterine meconium passage was not known and since, when meconium was passed, it was presented to the fetal surface in high concentration, considerable amniotic fluid having been passed with the amniotomy.

The umbilical cord and superficial skin tend to assume the color of the amniotic fluid and appear yellow, green, or bronze in tint. Vernix and nails, however, appear uniformly yel-

low, regardless of the color of the amniotic fluid. In intensely stained infants, the tongue, and posterior pharynx may be coated with meconium. The placenta tends to assume the color of the amniotic fluid. The pigment is deposited on the fetal surface and washes off readily under running water.

The skin of the infant so involved may be normal, or may show various degrees of desquamation. This is circinate or moth-eaten in type. The desquamation progresses proximally from the palmar aspect of the distal phalanx toward the palm, and outward from the metacarpal phalangeal joint. On the body it may be seen extending outward from the axilla and groin. On occasion the desquamation may be so severe as to approach that of the macerated stillborn fetus. This process cannot be due entirely to the presence of meconium, since desquamation may be seen in the presence of clear amniotic fluid and after apparently normal deliveries. However, in those patients desquamation is usually less extensive.

THE PIGMENTS INVOLVED IN MECONIUM STAINING OF THE INFANT

The absorption spectra of normal amniotic fluid, diluted meconium solution, and meconium-stained amniotic fluids were performed with the Beckman spectrophotometer (Fig. 1). These fluids show a peak in the region of 410 mμ. This represents the "Soret band," an absorption peak typical of compounds containing a porphyrin nucleus. This peak remains after ultracentrifugation at 27,000 r.p.m. for one hour, a speed calculated to throw down the mucopolysaccharides present in the solution.

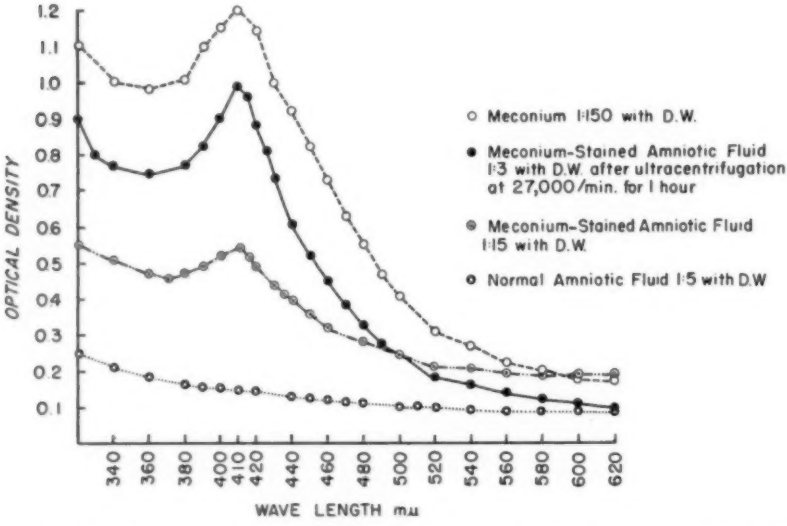

Fig. 1.—Absorption spectra of normal amniotic fluid, meconium-stained amniotic fluid, and meconium.

Normal amniotic fluid, meconium, and meconium-stained amniotic fluid

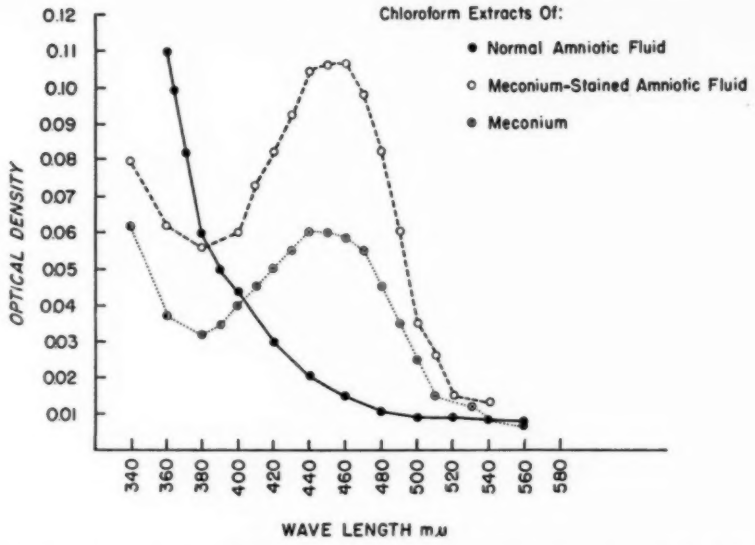

Fig. 2.—Absorption spectra of chloroform extracts of meconium, normal amniotic fluid, and meconium-stained amniotic fluid.

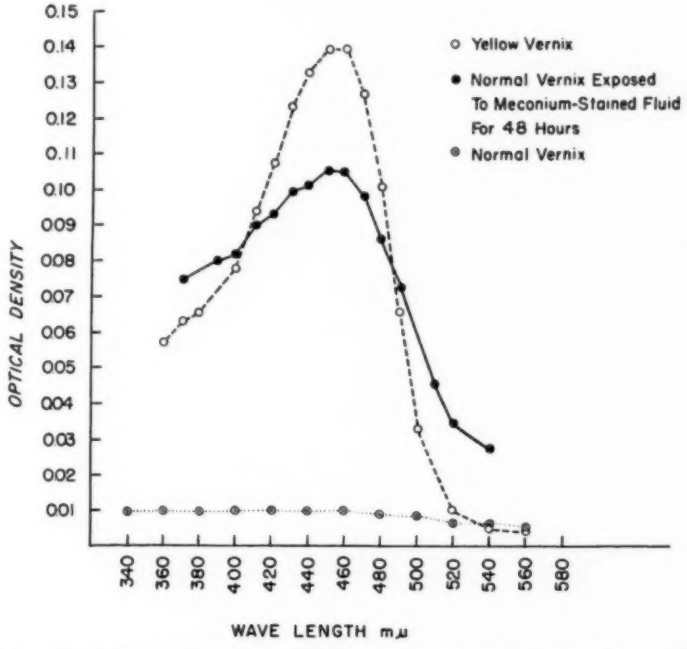

Fig. 3.—Absorption spectra of chloroform extracts of normal and yellow vernix.

were extracted with chloroform and passed through the spectrophotometer (Fig. 2). These extracts show a uniform peak at 460 mμ—a peak typical of commercial bilirubin. These extracts gave a positive reaction with the diazo and Fouchet's reagents, reactions typical of bilirubin. Alcoholic extracts of meconium and meconium-stained fluids gave a similar peak at 460 mμ.

Chloroform extracts were made of normal vernix, yellow vernix (from an infant born of a delivery in which meconium-stained fluid was present), and normal vernix incubated for forty-eight hours with meconium-stained fluid (Fig. 3). The latter two extracts also showed a typical bilirubin peak at 460 mμ.

Biliverdin is a known constituent of meconium and meconium-stained amniotic fluid. Attempts to demonstrate the presence of biliverdin in yellow vernix were unsuccessful in this laboratory.

It thus appears that vernix caseosa, suspended in a meconium solution which contains a mixture of pigments, selectively tends to absorb more of the yellow pigment. This may be due in part to the relative insolubility of the green pigment, biverdin. It has been shown that bilirubin has the property of penetrating the surface monolayers of cholesterol, a normal constituent of vernix caseosa. In addition, bilirubin possesses the capacity for binding to protein.[13] This property of bilirubin may possibly be the explanation for the yellow color of skin and nails seen after the infant's body has been suspended in meconium-stained fluid.

THE USE OF THE WOOD'S ULTRAVIOLET LAMP IN THE RECOGNITION OF MECONIUM STAINING

At the midpoint of the study it was noted that infants exposed to meconium-stained amniotic fluids showed some degree of dull orange-red fluorescence when placed under a Wood's lamp.* This fluorescence usually parallels the degree of visible staining but is more easily recognized, particularly when infants born after normal delivery are utilized as control subjects. The degree of fluorescence begins to fade within six to twelve hours after birth and is usually not present after twenty-four hours except in extreme cases (Plate II).

The type of Wood's light used was of the long-wave type (360 minute Hanovia type 10103*).

It is necessary that the infant's eyes be protected from the ultraviolet lamp during exposure. Under ultraviolet light the normal nail border and the umbilical cord appear bluish white and the intact skin purple. Desquamating skin appears white. Infants exposed to meconium-stained amniotic fluids for long periods show a dull orange-red fluorescence at the free nail border, periungal tissues, and over desquamating or macerated skin. Yellow vernix may or may not show this phenomenon.

When the nails of normal infants are exposed to meconium or to meconium-stained amniotic fluids, the progression of color development, as seen under the Wood's lamp, appears to be as follows: (1) the loss of the normal blue-white color of the nail, (2) the appearance of a dull tan color

*Hanovia Chemical and Mfg. Co., Newark, New Jersey.

Plate I.

Plate II.

Plate I.—Meconium staining of the newborn infant.
Plate II.—A drawing of the appearance of meconium staining under the Wood's light.

of nail and periungal tissues, and (3) the appearance of the characteristic orange-red fluorescence. The first stage usually appears before visible yellow staining may be seen in natural light.

Three hundred fifty consecutive infants were placed under the Wood's lamp. Six infants, in whose records the amniotic fluids were described as clear, showed some degree of change under the Wood's lamp. After having been checked with the obstetrician, the records were found to be in error in three cases. In the remaining three, the obstetrician did not recall the color of the amniotic fluid. Thus, the association of orange fluorescence with meconium staining of the amniotic fluid is a close one and it may be assumed that if this color is present under the Wood's lamp meconium or bile pigments were probably present in the amniotic fluid.

The color given by meconium must, however, be distinguished from that given by large dosage of the group B vitamins or the tetracycline antibiotics. It was noted that the nails, skin, and cord of some infants showed a striking greenish yellow fluorescence. This was of greater intensity than that shown by meconium staining. In each instance the mother had been treated with intravenous vitamin B or one of the tetracycline antibiotics within twenty-four hours prior to delivery.

Two mothers were given 1 c.c. of intravenous vitamin B complex (Betalake) in 5 per cent glucose infusion. At delivery eight and twelve hours later, respectively, the amniotic fluid was noted to be clear. Under the Wood's light, these fluids showed an intense yellow-green fluorescence. The infants' nails and cords showed a similar color. When tetracycline (500 mg. Achromycin) was given I.V. to two normal mothers twelve and twenty-four hours prior to delivery, the fluid showed a slight yellow coloration under natural light and marked green-yellow fluorescence under the Wood's lamp. The infants' nails and cords showed a marked greenish yellow fluorescence. This is easily differentiated from the dull orange seen after meconium staining.

The pigment or pigments responsible for the nail and skin fluorescence are not known. The probability is, however, that the color is due to porphyrin compounds which are known constituents of meconium.[12] In addition, it has been shown that porphyrin compounds, at physiologic pH, may be expected to couple readily to basic proteins.[11]

Coproporphyrin has been identified in the plasma of the fetus and newborn infant and in meconium. Needham[14] states that a physiologic porphyria is present during fetal life and can be ascribed to the vigorous hematopoiesis characteristic of this period. The majority of investigators[15] today agree that porphyrin formation normally occurs during hemoglobin synthesis and that the porphyrins found in feces represent intermediates or by-products of hemoglobin synthesis. It is believed that excessive quantities of Type I coproporphyrin result from an increase in rate of hemoglobin synthesis whereas accumulation and excretion of Type III tend to occur after interference with the synthesis of heme.[15]

Meconium and meconium-stained amniotic fluid usually show no fluorescence under the Wood's lamp.

However, two specimens of meconium did show a dull red-orange fluorescence directly. Qualitative tests for porphyrin were strongly positive in these instances. One of the infants had severe hemolytic disease (Rh) and one had polycythemia with a hemoglobin level of twenty-four grams at birth.

Subsequently, specimens of meconium, meconium-stained amniotic fluids, normal amniotic fluids, and vernix were extracted quantitatively for porphyrin content and separated by means of paper chromatography according to the method of Rappaport and associates[16] (Table II). The only porphyrin compounds identified in meconium and meconium-stained amniotic fluids were coproporphyrin I and III. These, however, were found in amounts greater than those previously reported in the literature.[17] Coproporphyrin I and III may not be the only fluorescent pigments present in these fluids, however, since in some specimens fluorescence was present up to but not following esterification with methanol hydrochloride.

TABLE II. THE CONCENTRATION OF COPROPORPHYRIN I AND III IN MECONIUM, AMNIOTIC FLUID, AND VERNIX

	NUMBER SAMPLES	COPOPORPHYRIN I (μG/ML. OR GRAM)		COPROPORPHYRIN III (μG/ML. OR GRAM)	
		AVERAGE	RANGE	AVERAGE	RANGE
Meconium	5	89	23-141	101	26-192
Meconium-stained amniotic fluid	5	2.7	1.4-3.7	2.2	0.9-3.6
Normal amniotic fluids	3	Traces		Traces	
Yellow vernix	3	Traces		Traces	
Normal vernix	2	None		None	

CONCLUSIONS

1. The incidence of meconium staining of the amniotic fluid in a series of 3,967 consecutive deliveries in a charity hospital was found to be 10.9 per cent. When corrected for blood incompatibility, high intestinal obstruction, and breech delivery, the incidence was 9.6 per cent.

2. Meconium staining of the amniotic fluid is associated primarily with the delivery of infants of term weight (96.4 per cent).

3. The neonatal mortality rate was 3.4 per cent and the neonatal morbidity rate 22.8 per cent, as compared with a neonatal mortality rate of 1.5 per cent and a morbidity rate of 6.1 per cent in the control group.

4. The time required for minimal nail staining to appear after exposure of the infants' nails to meconium-stained amniotic fluid is four to six hours. A longer period, twelve to fourteen hours, is required for staining of the vernix caseosa.

5. Infants exposed to meconium or meconium-stained amniotic fluid show a dull orange-red fluorescence under the Wood's ultraviolet lamp. This procedure may be of help in the recognition of these infants. The color produced may be due to the presence in meconium of coproporphyrin I and III which has penetrated nails and skin. This color must be differentiated from the glowing yellow-green fluorescence found on the infant's nails, cord, and skin after the mother has undergone recent therapy with

vitamin B complex or the tetracycline group of antibiotics.

6. The pigment staining the nails and vernix may be bilirubin.

We wish to thank the nurses, residents, and interns who cooperated in this study and made it possible. The authors express appreciation to Dr. J. Gast, Dr. D. Rappaport, and Mrs. Catherine Calvert for the use of their facilities and for assistance with the porphyrin determinations.

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Sudden Deaths in Infancy

Oct. 31, 1740. A daughter of Thomas Dibble Jr aged about 2 months—just about an hour before it was left in bed as well to appearance as ever but lying still when they went to look at it found it dead—since, I was told it was well in the evening and when the mother got up, she laid it on her arms thinking it was asleep & about an hour after found it dead & stiff probably died in the night.

March 7, 1741. A Son of Jonathan Conkling aged about 6 weeks died in the night by her mother—not knowing when it died.

DEATH RECORDS of Easthampton, New York.

NONPUERPERAL LACTATION IN GRANDMOTHERS

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THE practice of middle-aged women putting their grandchildren to their breast and encouraging them to suck has been described as occurring among some peoples.

The ability of these grandmothers to produce breast milk is of interest, and several examples of this have come to my notice in our family practice at the Polela Health Centre, Natal. A cursory enquiry has revealed ten cases in which women have breast fed their grandchildren. Five produced breast milk and three of these are lactating at present. These cases are briefly described.

CASE REPORTS

CASE 1.—This woman, born in 1906, bore five children, the last being born on April 28, 1941. She successfully breast fed all for varying periods of up to two years, having weaned her last in 1943.

Her daughter had three children and weaned her last child, born May 26, 1954, at the age of 2 months, as she had to return to her employment.

Grandmother put this baby to the breast on the day of his mother's departure (July, 1954) and encouraged him to suck, in an effort to comfort him in his distress. (This use of the breast as a comforter is the expected practice among all Zulu women of this Polela area.) She noticed the appearance of breast milk twenty-four hours after the start of this sucking, and this lactation has continued to the present time, for a total period of nineteen months (Fig. 1).

Thus a woman, aged 48 at the time, who had weaned her own last child eleven years previously, has suckled her daughter's baby from the age of 2 months for 19 months. A further interesting feature is that her menses were regular until three months after she began breast feeding this grandchild, and have since ceased.

Whether this is her menopause or a reaction to lactation cannot yet be decided. It will be interesting to follow her further when she stops lactating.

CASE 2.—Born in 1908, this woman breast fed her own children for over one year each, weaning her last child (born in July, 1934) in 1936. She has suckled all her daughter's children and lactated freely each time. This has been indulged in, even in the presence of her daughter, but initially was started in an effort to pacify the children during the temporary absence of their mother.

The first grandchild was breast fed from 1951 (i.e., fifteen years after the weaning of her last child) to early 1952. The second, born in November, 1951, was weaned from the mother in November, 1952, and then breast fed by the grandmother until the end of 1953.

The last grandchild, born Aug. 26, 1954, is at present breast fed by both mother and grandmother.

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*Formerly Medical Officer-in-Charge, Polela Health Centre.

Breast milk was secreted by the grandmother one week after she had first put him to the breast. Her menses were not affected by these periods of lactation.

CASE 3.—Born in 1907, this subject bore twelve children and successfully breast fed nine for periods of over one year, the other three having died as neonates. Her last child was weaned in January, 1950. She put her daughter's first child (born April 15, 1951) to her breast at the age of 1 year, during the absence of his mother, because "she did not want him to cry." He sucked for "only a few minutes on the first day, and breast milk was secreted on the following day." She maintained this breast feeding for two months, weaning him in June, 1952.

Fig. 1.

In March, 1954, when her second grandchild was 2 months old, she put him to the breast to pacify him. On the "first day, the holes of the nipples were closed, the next day only water appeared, and milk came in fair amounts on the third day." She reports that she had been suckled by her own grandmother, and her nine children had been breast fed by their grandmother, i.e., her mother, who was able to produce milk for each grandchild.

Her menses remained unaffected during these periods of lactation.

CASE 4.—Born in 1909, the subject successfully breast fed all four of her own children, weaning the last-born in 1951. At that time she was still lactating. She put both of her grandchildren to the breast, but at no time noticed any breast milk.

The second grandchild, born Aug. 9, 1954, was put to her breasts in April, 1955, when the mother returned to her employment.

She had not noticed breast milk during this period, and showed surprise at the breast milk which could be expressed manually, with ease.

Her own mother had comforted her daughter with the breasts, when she had had to return to work, but no milk had been seen.

CASE 5.—Born in 1906, and in her postmenopausal period, this grandmother put her second grandchild (born in 1953) to her breasts during the day in the absence of his mother. The child's mother, however, breast fed him at night.

No breast milk has appeared in the grandmother's breasts. This comforting was practiced for about three years, even after his mother had weaned him.

During this period, and up to the present, this child has referred to his mother as "uSisi" (sister) and called his grandmother "uMa" (mother). In contrast, his elder brother, born in 1950 and breast fed by his mother only, calls grandmother "uGogo" (granny) and the mother "uMa."

DISCUSSION

The ability of these middle-aged Zulu women to produce breast milk, even many years after pregnancy and the weaning of their own youngest children, seems to be dependent upon

their use of the breast as a comforter to quiet the grandchildren. The appearance of the milk in these grandmothers would appear to be a direct response to this practice.

Of interest is the handing down of this practice through the generations in two of the examples, and the short period of sucking necessary to stimulate the breasts of one woman.

Bryant[1] described a few similar examples among the Bantu tribe, of "quite old women, even grandmothers of the infant (and themselves long beyond their menopause and ability to bear children of their own) able to excite their mammary glands to the production of milk" and thereby suckle and rear the babies.

More recently, Barlow and Buchan[2] mention another example in Lusikisiki, Cape.

It is probable that this practice is dying out, as it is scoffed at by most of the present generation of mothers. As one mother put it, "Of what use to the baby is a shriveled old breast?"

However, it would appear that suckling of grandchildren by rural Zulu women is still not rare.

SUMMARY

1. Of ten Zulu women who had put their grandchildren to the breast, five produced breast milk in response to the sucking.

2. The secretion of milk occurred some years after their last pregnancies.

I am indebted to Professor Sidney L. Kark of the Department of Social, Preventive and Family Medicine, Natal University, for his help and to Medical Aide O. P. S. Mdala of the Polela Health Centre for the photograph.

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Gravestone in West Springfield, Mass.

Nathaniel Parks, died March 21, 1794, aged 19. "He was out a hunting and was casually shot."

CHRONIC STAPHYLOCOCCAL ENTERITIS IN INFANTS

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THE *Staphylococcus aureus,* variously called coagulase-positive staphylococcus, *Micrococcus pyogenes* var. *aureus* or *albus,* or *Staphylococcus pyogenes,* and henceforth referred to only as staphylococcus, has always been a troublesome organism and has become even more troublesome to both clinician and bacteriologist since antibiotics came into common use. It has demonstrated an amazing ability to change its various characteristics and a remarkable adaptability to adverse circumstances. These characteristics manifest themselves not only in the development of resistance to antibiotics and chemotherapeutic agents, but also in ways more easily appreciated only by the bacteriologist, such as loss of ability to produce pigment and as variations in colonial morphology, to quote but two examples. These potentialities pose the question as to whether there may not also be changes in pathogenic qualities. This interesting possibility finds support in the emergence of a clinical pattern which it is the purpose of this article to describe.

In 1951 Finland[1] drew attention to enteritis occurring as an acute disease after the use of antibiotics. Karelitz[2] mentions staphylococci as a cause of diarrhea, presumably acute, in infants. The cases to be described here, however, showed a chronic disease pattern, and the fact that the great majority of them were referred in consultation leads one to believe that the staphylococcus as a cause of chronic digestive tract disease is not commonly appreciated. It is this fact more than any other which has led to the recording of this condition, as it is felt that the earlier treatment is started, the more easily a good result is obtained.

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THE CLINICAL SYNDROME

The complaint is usually of diarrhea with foul-smelling stools containing mucus and sometimes blood, occurring in an artificially fed infant. The infant is likely to be fussy but is not acutely ill, and the case is usually treated as a feeding problem. Frequently there have been several changes of formula without benefit. On inquiring into the history, it may be found that the symptoms have been present since discharge from the nursery, or shortly after that.

There follows a brief description of nine cases in chronological order. Except where specifically mentioned these infants were born in the Calgary General Hospital. All the infants were artificially fed.

CASE REPORTS

Case 1.—B. Y., female, aged 4 weeks, was apparently well for one week after leaving the hospital and then developed diarrhea with occasional vomiting. The symptoms con-

tinued off and on for a further three weeks, during which time several different formulas were tried without apparent benefit. Two days before readmission, blood was noted in the stools and diarrhea became intense. On admission to hospital she was given oral streptomycin, but when she did not improve a stool culture was done. It showed the presence of staphylococci. She was given intravenous erythromycin and responded well. She was discharged on the eleventh hospital day, and remained well for several months, when she left the district.

CASE 2.—W. P., male, born Nov. 16, 1954, was a premature infant weighing three pounds, two ounces. He was first seen shortly after birth, because of cyanotic spells, which continued in spite of treatment intermittently for about a week. Because of failure to thrive, infection was suspected on clinical grounds on November 22, and he was given oral erythromycin. No further clinical signs were noted until November 29, when he developed loose stools. These continued and on December 8, he was put on tetracycline orally but without improvement. On December 11, he was found to have a septic finger, from which staphylococci were grown. On December 12, he was given chloramphenicol orally, but his condition deteriorated and he died on December 14. Autopsy (twelve hours after death) showed a bronchopneumonia from the purulent exudate of which staphylococci were cultured. The mucosa of the jejunum was edematous, velvety, and red, these characteristics diminishing gradually toward the lower end of the ileum. There was also considerable ulceration. On histological examination the jejunum and ileum both showed coagulated necrotic mucosa with a massive growth of coccal colonies. The submucosa was found to be frequently edematous and to show a moderate lymphocytic infiltration. Regional lymph nodes showed acute inflammation. Staphylococci were grown from the lungs and from the intestine. It is interesting to note that two different strains of staphylococci with different sensitivity patterns were eventually identified in this case.

CASE 3.—A. J., female, aged 13 days, was readmitted to hospital because of loose stools which had been present since before she left the hospital nursery on the seventh day. She had no vomiting but had been unduly fussy. Staphylococci were grown from the stools. She was given chloramphenicol, streptomycin, and erythromycin and improved symptomatically, so that she was sent home on the eighth hospital day. The diarrhea recurred as soon as she was home and she was readmitted the following day. Staphylococci were again grown from the stools. She was given erythromycin for six days and again discharged. She had some symptoms of colic thereafter, but essentially has remained well. Probably the recurrence was due to insufficient length of treatment in the first place.

CASE 4.—B. D., male, aged 3 months. The complaint in this case was of diarrhea with blood and mucus in the stools for two weeks. On further questioning later the mother said that his stools had never been like those of his elder brother. She also complained of his being excessively fussy and not sleeping well. Two weeks before the onset of the symptoms he had a respiratory infection which settled but left him not so well as he had been before. At first this baby was thought to have steatorrhea, but there were no confirmatory signs of this. Erythromycin was given for six days and then, when a stool culture grew staphylococci, he was given chloramphenicol. He was discharged improved after six days on this drug. He was readmitted five days later and this time was given intravenous erythromycin for a further seven days. There were no staphylococci in the stool on discharge. He was readmitted twenty-four days later, because staphylococci had again been found in the stool in association with diarrhea, and on this occasion was given streptomycin without apparent benefit, although he improved to a

certain extent without specific therapy. One month later he had a single episode of passing blood and mucus in the stool but remained relatively well. A barium enema at this time showed no ulceration in the region examined, i.e., the large intestine. Five months later he had a severe upper respiratory infection with otitis which responded to treatment with oxytetracycline, but ever after this he has had loose stools with mucus. In three weeks' time this had become so bad that he was readmitted and again staphylococci were found. The symptoms on this occasion responded well to streptomycin and penicillin. Another barium enema showed a negative result. Since this time he has had staphylococci in the stools from time to time and his loose stools have recurred.

CASE 5.—G. L., male, aged 1 month, was apparently well till 1 month of age, when he became excessively fussy and started to regurgitate feedings. Two days after the onset of symptoms he was admitted to hospital, where a diagnosis of pylorospasm was made. Response to treatment with an atropine homologue was good. He was discharged, well, on the fifth hospital day, but three days later he was readmitted with a history of diarrhea but no vomiting, of three days' duration. The stool culture showed staphylococci. He appeared to respond well to chloramphenicol and was discharged on the fifth hospital day. He immediately left the district, so that follow-up was not possible.

CASE 6.—L. D., male, aged 4½ months. This child's history was one of vomiting, diarrhea, and gas pains, of six weeks' duration. The symptoms were gradual in onset and appeared at first to respond to a sulfonamide, but then recurred, reaching an intensity just before admission. Stool culture showed staphylococci. He was treated with streptomycin with apparent response but then relapsed. After two weeks in hospital with no appreciable progress he was given intravenous erythromycin for three days, followed by oral erythromycin. He was discharged, well, two weeks later and has remained well since.

CASE 7.—N. S., aged 6 weeks, was one of twins born in the Holy Cross Hospital, Calgary. At 2 weeks of age the stools were noted to be loose and foamy. Several changes of formula were tried and did not produce any improvement. Stool culture showed staphylococci. She was given chloramphenicol. The following day she left for Europe, so no follow-up was possible.

CASE 8.—E. F., male, aged 4 months, had had loose stools from the time he was in the nursery, but otherwise had been well and had thriven to a certain extent. A stool culture was taken but no pathogens were found. Dietary treatment was therefore tried but was without beneficial effect. One month later another stool culture was taken and staphylococci were grown. He was given oral erythromycin and within a few days the stools became normal and have remained so, and his general nutrition has improved remarkably. It was later realized that no differential media had been used for the first stool culture.

CASE 9.—M. W., female, aged 5 weeks, was born in a small country hospital. She had diarrhea since going home. There was also excessive fussiness and she had had several changes of formula. Stool culture showed staphylococci. She was given erythromycin orally for ten days. Eighteen days later it was reported that the diarrhea had settled down in a few days and her bowel movements had remained normal.

In all these cases the antibiotics used were those indicated by the disc sensitivity tests.

The first of these cases was not considered remarkable at the time the diagnosis was made. The autopsy findings of the second case were considered rather unusual but not particularly out of the ordinary. However, when the third and fourth cases

turned up and it was found that the condition was occurring quite frequently, more interest was taken in the syndrome and from then on it was possible in most of the cases to suspect the etiology before bacteriological proof became available. Cases 7, 8, and 9 were all diagnosed in such a manner, and hospital treatment was not necessary to effect a cure. Thus it is quite possible with a little clinical experience to diagnose these cases early. Perusal of the case histories indicates that early diagnosis appears to render treatment more likely to be successful immediately, as illustrated by Cases 5 and 9. Late diagnosis, on the other hand, appears to make treatment difficult, as shown by Cases 4 and 6, although Case 8 demonstrates that this is not always so.

DISCUSSION

The constant association of this syndrome with the presence of staphylococci in the stools is strong presumptive evidence of the etiological relationship. This is further supported by the response to relatively specific treatment, and the absence of other known pathogens in the stools.

Why should it be that staphylococci are responsible for a moderately common condition which has hitherto caused little comment in the literature? The answer must lie in one of two reasons: either the condition is really becoming commoner, or we are becoming more aware of different manifestations of staphylococcal infections. As regards the first possibility this is almost impossible to prove, but it is made likely by the enormous increase in staphylococcal carrier rates in the hospital population. As regards the second possibility, there is no doubt that the widespread introduction of selective media for the isolation of staphylococci from stools has made diagnosis more reliable and easier. (In these cases 7.5 per cent NaCl was used as the inhibitor in agar base media.) The true answer may well be a combination of these two factors.

From the clinical viewpoint this disease appears in some instances at least to have been contracted in the maternity nursery. In Case 5 it is apparent that the infection was acquired in the pediatric ward. Carrier rates and morbidity rates have been investigated on numerous occasions in the past few years. For instance, Edmunds and associates[3] give a carriage rate of 35.3 per cent in the eye and 40.1 per cent in the umbilicus and a morbidity rate for eye and skin of 9.8 per cent and 4.8 per cent, respectively. They do not, however, report the stool carrier rate and there is no mention of enteritis.

Because of the clinical grounds for suspecting the infection to occur in the nursery, a week was chosen at random, during which all babies discharged from the nursery had stool samples cultured for the presence of staphylococci. There were forty-three babies discharged during this particular week, and in ten of them coagulase-positive staphylococci were found in the stools (23.3 per cent). Yet Dearing and Heilman[4] in 1953 state that staphylococci are normally present in feces only rarely, and are never seen in large numbers. They assume that staphylococci may pass from the upper respiratory tract when the gastrointestinal tract is under the influence of an antibiotic. Here, however, we are dealing with babies who have not been exposed to an antibotic. There may be a certain analogy, in that both the

newborn infants and the older persons under treatment with antibiotics are relatively lacking in the usual intestinal flora. This absence of antagonists may allow the staphylococcus to establish itself in the intestine and produce symptoms sooner or later in the absence of immunity or when conditions are otherwise opportune. The immunity of babies must be very variable. According to Smith[5] an infant appears to have no immunity to staphylococci, but in the face of the high incidence of asymptomatic carriers this must be a generalization with many exceptions. Topley and Wilson[6] even give an antibody titer of 0.25 to 0.75 U. per milliliter for normal human adults and newborn infants. It is interesting to note in this connection that none of the ten neonates mentioned developed symptoms up to the age of 6 weeks and that seven of them were breast fed.

The only fatal case showed that the staphylococci were deeply embedded in the intestinal mucosa. It cannot be inferred from this that the same happens in all cases, but nevertheless there are some grounds for believing that it does happen at least in the more chronic cases. It may be an indication, too, that one should not expect drugs to exercise a beneficial effect locally in the intestine, but rather that systemic antibiotics ought to be given, to approach the organism via the blood stream. If the diarrhea is severe, the drug should be given parenterally to avoid poor absorption. This method certainly seemed to be effective in Cases 4 and 6.

Finally, the high carrier rate even in the newborn infants shows that the mere presence of these organisms in the stool must not be taken as an absolute indication of staphylococcal enteritis and that other causes, such as allergies or parenteral infection, may be responsible for the intestinal symptoms. This high carrier rate is also obviously of importance in the management of a nursery. Since the disease appears to be on the increase, at any rate in this region, there is all the more reason for attempting to prevent it at its source.

SUMMARY

A clinical pattern of digestive tract disorders occurring in infants is described, which appears to be caused by staphylococci. It is felt that the original infection occurs in the neonatal period and that the earlier the diagnosis is made, the more effective treatment is likely to be. While the symptoms are often mild, yet they should not be overlooked, as the disease may be responsible for chronic ill health. It is therefore recommended that in dealing with cases of diarrhea in infants in the first few months of life, stool cultures should be taken with the precise idea of searching for staphylococci.

Thanks are due to Dr. G. B. Elliott for his cooperation and to Mrs. E. Levine for technical assistance.

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FRAGILE BONES AND MACROCRANIUM

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THIS is the report of a child who showed an unusual combination of manifestations: repeated fractures with deformities starting early in life, osteoporosis, and a greatly thickened skull.

CASE HISTORY

Carmen R., a 5-year 4-month-old Puerto Rican girl, was admitted to the orthopedic service at Bellevue Hospital on May 16, 1953, because of multiple fractures of the long bones with resulting deformities.

She was born in Puerto Rico at term, the older of two children. Delivery and postnatal course were uncomplicated. Owing to incompatibility the parents separated, the mother remaining in Puerto Rico with a younger sister, the father coming to the United States. The father had a "mental disease," the mother was living and well. The youngster lived here with her paternal grandparents with whom she had a warm relationship. The maternal grandfather was diabetic. The younger sister, 3 years of age, had a fracture of a lower extremity after trauma. There was no family history of multiple fractures, blue scleras, or deafness.

Progress during early infancy was normal. The first fracture, of a lower extremity, took place before the end of the first year of life. Subsequently fractures of the long bones of both upper and lower extremities occurred at a rate of about two per year for which she was admitted to various hospitals. She began to walk at one year. Bowing of the lower extremities was first noticed at 3 years. The upper extremities also became bowed. The patient was able to run about and take care of herself. She spoke well. At about 3 years enlargement of the head was observed. She never had severe abdominal pain or kidney stones.

On examination Carmen appeared normally intelligent. She was a rather surly, quiet child. She walked with a stoop and with short steps, using little flexion of the extremities. The head was large in all dimensions. The femurs, humeri, and leg bones showed saber-like deformities. The chest was short and deep anteroposteriorly. The scleras were white.

The laboratory findings in 1953 were as follows (all values are expressed per 100 c.c. unless otherwise indicated):

Hemoglobin	11 Gm.
Erythrocyte sedimentation rate	12 mm./hour
Serum calcium	11.2 mg.
Serum inorganic phosphate	6.0 mg.
Serum alkaline phosphatase	6.4 Bodansky units
CO_2	22.3 meq./L.
Total serum protein	7.6 Gm.
Total serum albumen	5.3 Gm.
Total serum globulin	2.3 Gm.

Carmen was discharged from the hospital on Aug. 4, 1953. She continued to have fractures and was readmitted to Bellevue Hospital on Aug. 23, 1955, because of a fracture of the upper third of the right femur incurred while playing in the street.

At this time she was an alert, intelligent, dark-skinned Puerto Rican girl (Fig. 1). She was 7 years 7 months of age. The head was symmetrically enlarged with frontal bossing.

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The head and face measurements are shown in Table I.

TABLE I

DIMENSION	PATIENT (CM.)	NORMAL MEAN (CM.)	NORMAL S.D. (CM.)
Circumference of the head	60	52	1.25
Lateral diameter of head (bitemporal)	15.1	13.9	0.5
Occipitofrontal diameter of head	20.6	17.7	0.7
Bimalar diameter of face	11.7	5.4	0.75

The genitals were normal. The extremities showed marked bowing of all the long bones. The hands appeared normal. The neurological and fundus examinations were negative.

Laboratory Findings.—The laboratory findings are given in Table II. All values are expressed per 100 c.c. unless otherwise indicated.

The serum calcium and phosphorus were in the normal range. On admission, when the youngster had a fresh fracture, the alkaline phosphatase was elevated (23.7 Bodansky units), but

Fig. 1.—Patient at 7 years 7 months. The stance is crouching. The head is large in all diameters. The face is also large. The extremities are bowed.

The skin was clear, the scleras white. There was moderate scoliosis and lordosis of the spine with pronounced curvature of the ribs and a deep chest. The costochondral junctions were not felt. The heart sounds were of good quality but distant. The abdomen was soft, without distention or masses.

it fell to normal levels when healing took place. The urine Sulkowitch test gave a persistent 3 plus reaction.

An unusual finding was a serum protein value of 8.1 grams per cent. Fractionation of the serum proteins by electrophoresis showed elevation of the alpha-2 globulin fraction.

The serum ester cholesterol was reduced on two examinations, in one instance to 54 per cent of the total, in the other to 31 per cent. A later determination showed a rather high total cholesterol (312 mg.), the ester cholesterol 227 mg.

Roentgen Examination in 1955.—The frontal, parietal, and occipital bones were uniformly widened, owing to deepening of the diploic space, and measured 2.5 cm. in diameter. The inner plate of the skull bones was of normal thickness, the outer plate was thin but well defined. The skull was osteoporotic and granular in appearance. The bones of the face were normal.

TABLE II

Blood	
Hemoglobin	12.0-13.5 Gm.
Red blood cells	4.6 million per c.mm. Cells normocytic, normochromic
Platelets	Normal
White blood cells	14,600 per c.mm.
Polymorphonuclears	33%
Lymphocytes	61%
Monocytes	5%
Eosinophils	1%
Hematocrit	33-41%
Sickling	Negative
Electrophoresis	Normal adult hemoglobin
Mazzini	Negative
Serum calcium	9.1-11.2 mg.
inorganic phosphorus	3.1-6.0 mg.
alkaline phosphatase	5.9-23.7 Bodansky units
protein (total)	8.1 Gm.
albumen	4.4 Gm.
globulin	3.7 Gm.
Plasma electrophoresis	Slight increase in alpha 2 globulin
Total cholesterol—280 mg.	Ester cholesterol—87 mg.
Total cholesterol—256 mg.	Ester cholesterol—139 mg.
Total cholesterol—312 mg.	Ester cholesterol—227 mg.
Sodium	142 meq./L.
Chloride	107 meq./L.
Nonprotein nitrogen	29.3 mg.
Icterus index	6 units
Thymol turbidity	3.9
Urine	
Specific gravity	1.015-1.026
pH	5.5-7.5
Albumen	Negative
Sugar	Negative
Acetone	Negative
Sulkowitch	3+
Paper chromatography	Normal pattern
Phenolsulfonphthalein test	Normal

Because the skull changes resembled in many respects the appearance seen in some of the anemias, the blood was studied carefully. There was no anemia. At no time was sickling observed, even after the addition of sodium meta-bisulfite. Electrophoresis failed to reveal any abnormal hemoglobin. Bone marrow examination was normal.

The long bones were distorted, presumably owing to the healing of numerous fractures (Figs. 2, 3, 4, 5, 6). The femurs, humeri, and leg bones were markedly bowed. The bony texture was irregular. The bones were

Fig. 2.—The skull is greatly thickened. The inner table is well defined and heavy; the outer table is thin and fairly well defined. The bones of the face are normal.

Fig. 3.—The humerus is markedly bowed. The bones are osteoporotic and the outlines are irregular.

Fig. 4.—The bones of the hand are expanded and osteoporotic with coarse markings. The tubular bones show well the widening due to dilatation of the medullary cavities.

Fig. 5.—The femurs are markedly bowed and osteoporotic.

Fig. 6.—The right tibia and fibula show anterior bowing, marked osteoporosis, coarse transverse markings, subperiosteal ossification over fibula.

Fig. 7.—Osteoporosis of the vertebrae. Marked scoliosis.

osteoporotic with coarse striations, principally longitudinal. The tubular hand bones were expanded and osteoporotic. The vertebrae, ribs, scapulae, and clavicles were also osteoporotic with heavy linear markings. There was well-marked scoliosis (Fig. 7). Similar changes were present in films taken in 1953.

Pathology.—Bone specimens were removed from the left tibia and from the right iliac crest and examined by Dr. Henry L. Jaffe, pathologist at the Hospital for Joint Diseases, New York. Dr. Jaffe's report is as follows:

"The tissue slide representing material removed from the left tibia shows a fragment of lamellated cortical bone. The covering periosteum is thickened and its inner layer (the osteal cambium layer) is quite cellular. One notes also evidence of subperiosteal new bone apposition which is reflected also in the roentgenograms of the various bones. The osseous tissue representing the cortical bone is abnormal in several ways. First of all, the trabeculae making up the cortex show a good deal of osteoclastic resorption on the surface toward the periosteum. On the surface away from the periosteum, there is new bone deposition and on that surface in particular the trabeculae are lined by an almost continuous layer of osteoblasts. Furthermore, the trabeculae making up the cortex, while composed of lamellar bone, fail to show more than an occasional Haversian canal. In other words, the cortical bone has the architecture ordinarily seen in lamellar bone. The wide spaces between the osseous tissue contain a rather edematous, loose, and vascular connective tissue substratum.

"The tissue slides representing biopsy material from the right iliac crest show that the osseous tissue is everywhere undergoing spotty osteoclastic resorption and, concomitantly, there is new bone deposition. In some places, a pattern suggestive of the mosaic pattern of Paget's disease is being built up. In the tissue sections of the material removed from the iliac crest, there is again no striking fibrous reaction in the spaces between the osseous trabeculae.

"The question is how to correlate these histologic findings with the roentgen findings. To some extent, the roentgenograms of the long bones could be considered as representing a peculiar form of osteogenesis imperfecta. In Fairbank's *Atlas of General Affections of the Skeleton,* there are pictures in the chapter on osteogenesis imperfecta that simulate the appearances in the bones in this case. However, though he does show one skull picture in which there is thickening of the calvarium in a case of osteogenesis imperfecta, the alterations in the skull in this case are somewhat different. Part of the skull changes are of the same general character as those in the long bones, and possibly such changes do occasionally appear in atypical cases of osteogenesis imperfecta. I understand that there is no evidence of sickle-cell or Mediterranean anemia in this case and those conditions can be excluded as the basis for the bone changes. Also, I do not believe that the bone changes can be interpreted as a form of juvenile Paget's disease. All in all, then, on the basis of the tissue findings and the clinical history and the x-ray findings, the case is to be interpreted as a peculiar or atypical form of osteogenesis imperfecta."

DISCUSSION

The history of repeated fractures, starting during the first year of life, with generalized bony deformities suggests a diagnosis of osteogenesis imperfecta or fragilitas ossium. Some of the radiologic changes in the bones are compatible with this diagnosis. The absence of blue sclera and a family history of frequent fractures is customary in this disease when it starts early in life.

However, two unusual features practically exclude this diagnosis, the wid-

ening of the medullary cavities in the unfractured bones and the great thickness of the calvarium. These features have not been reported in any of the cases of fragilitas ossium. Fairbank[1] described a patient with osteogenesis imperfecta who showed irregular hyperostosis affecting both tables of the skull in the frontal and parietal regions, but the appearance was altogether different from that observed here.

The wide diploic space is similar to that sometimes seen in children with severe long-standing anemia. However, the child had no anemia at any time while she was under observation and she had no abnormal type of hemoglobin.

The long bone changes in our patient resemble somewhat those seen in Paget's disease, but the skull changes are quite different. In Paget's disease the outer table is generally thickened and increased in density and the skull appears coarsely mottled.

This patient's history and films were reviewed by Dr. John Caffey. It was his opinion that, in view of the expansion of the medullary cavities of the unfractured bones, in the hands especially, and the widened diploic space, this case should not be considered one of osteogenesis imperfecta.

SUMMARY

A child is described with multiple fractures beginning in the first year of life, bowing of all four extremities, and a large head.

Roentgen studies revealed greatly thickened frontal, parietal, and occipital bones with deepened diploic spaces, generalized osteoporosis, healing and healed fractures with bowing and angulation of all the long bones, and widening of the medullary cavities in the unfractured bones.

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Rough on Young M.D.'s

Deaths in Salem, Massachusetts, 1808.

July 6 Edward, child of Nathaniel and Abigail Chever. Suddenly, 18 months. Complaint in the bowels, pink root administered, and almost instant death ensued. Physicians both young.

July 6 John, son of John and Eunice Harwood. Suddenly. 31 months. As in the other case; complaint in the bowels, pink root administered, and almost instant death ensued. Same physicians.

THERAPY OF ACUTE PURULENT OTITIS MEDIA AND PURULENT TONSILLITIS WITH DIBENZYLETHYLENEDIAMINE DIPENICILLIN G

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IN THE search for an ideal therapeutic agent for the treatment of purulent otitis media, extensive studies have been made on all the antibiotics and chemotherapeutic agents.[1-3] Recently dibenzylethylenediamine dipenicillin G has been advocated by Walker[4] as the therapy of choice, inasmuch as it requires only one injection and provides adequate therapeutic blood levels up to fifteen days after administration. This prolonged high blood level has been demonstrated as necessary because of the frequent relapses following short-term therapy of otitis media.

To evaluate the drug in our own practice, we elected to give it to 100 patients with otitis media and/or tonsillitis. The patients were all children under the age of 14 years seen in the pediatric clinic of the Southern California Permanente Medical Group in Fontana, California, by one or the other of us. All patients had acute purulent otitis media, exudative tonsillitis, or both. After the diagnosis had been made, each child was given 600,000 units of dibenzylethylenediamine dipenicillin G by intramuscular injection. The condition of the patients prior to therapy is listed in Table I. An attempt was made to examine each child seven days after therapy for evaluation; however, some children were returned by their parents within three days because of progression of symptoms or lack of improvement, and some did not return as directed. All children who were not examined at the end of seven days were subsequently examined and found to be completely well.

TABLE I. CONDITION OF PATIENTS BEFORE THERAPY

Age in years, range	3 mo. to 14 yr.
Duration of disease in days, range	1 to 10 da.
Duration of disease in days, average	2 da.
Temperature in ° F., range	98° to 104.4°
Temperature in ° F., average	100.8°
Rupture of tympanic membrane, total	10
Per cent of patients with otitis media and rupture of tympanic membrane	13%
Prior administration of other antibiotics	None

RESULTS

The results, as summarized in Table II, are broken down into two categories: (1) those patients cured or improved within seven days after initiating therapy; (2) those not recovered or becoming worse in three to seven days after the initiation of therapy. There was a 23 per cent failure rate for those patients with otitis media, with

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A portion of dibenzylethylenediamine dipenicillin G (Bicillin) was kindly supplied by Wyeth, Inc.

or without tonsillitis; and a 7.7 per cent failure in patients with tonsillitis alone. This differs from a recovery rate of 100 per cent reported by Walker after similar therapy.

TABLE II. RESULTS OF THERAPY

PATIENTS WITH OTITIS MEDIA	
Total, with or without tonsillitis	74
Total failures (not improved, or worse, three to seven days after therapy)	17
Percentage of failures	23
PATIENTS WITH TONSILLITIS ALONE	
Total	26
Total failures (not improved, or worse, three to seven days after therapy)	2
Percentage of failures	7.7

DISCUSSION

The results of this study show a significant number of treatment failures from this type of therapy. Although no control study was done using another form of penicillin, it is possible that the bacterial flora in our population group would have been resistant to other forms of penicillin also.

We felt that one of the chief disadvantages of the drug was the severe and persistent pain at the site of injection. No accurate record was kept of the number of reactions, but many parents reported that the children were unable to walk or sleep, for two to three days, because of this pain. Many children were so fearful upon returning to the clinic that it was difficult to examine them again. In our experience the children will more readily accept procaine penicillin G in oil with aluminum monostearate* given for three or four injections on alternate days. This is especially true if the site of injection is iced prior to its administration. This prevents even the needle pain. The cost is not great and high blood levels can be maintained for ten days or longer. This of course is not ideal and for those who fail to respond, it is necessary to do cultures, sensitivity studies, and to switch to more specific antibiotic or chemotherapeutic agents.

CONCLUSION

A single injection of 600,000 units dibenzylethylenediamine dipenicillin G did not appear to constitute an ideal therapy for the treatment of acute purulent otitis media and/or tonsillitis. The incidence of failures in this group of patients with acute purulent otitis media was 23 per cent. A number of patients complained of severe pain at the site of injection. The results are less favorable than those reported in a similar study by Walker.

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AN ELECTROCARDIOGRAPHIC STUDY OF UNCOMPLICATED PERTUSSIS

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ELECTROCARDIOGRAPHIC abnormalities have been described in a variety of infectious diseases. For some years patients with bacterial and viral infections admitted to the Haynes Memorial Hospital have been subjected to serial study with the electrocardiograph as part of a systematic study of the effect of this type of disease on the heart. Abnormal tracings and anatomical evidence of myocardial involvement have been observed and reported in diphtheria,[1] scarlet fever,[2, 3] poliomyelitis,[4] and measles.[5] It is the purpose of this paper to report the results of a similar study in patients in the paroxysmal phase of pertussis.

Lapin[6] has credited Koplik with first calling attention to dilatation of the right side of the heart in whooping cough. This has also been noted by a number of other observers, but, as Lapin[6] has pointed out, all patients who have shown this abnormality had secondary bacterial infections of the lung or other pulmonary complications. In 232 cases of uncomplicated pertussis studied by Ledbetter and White[7] in which electrocardiograms were not taken, no detectable cardiac complications were noted. They commented on the fact that, although serious secondary pulmonary involvement might strain the right ventricle, they had observed individuals with pre-existing rheumatic or congenital heart disease who survived whooping cough without an increase in symptoms or signs of the underlying cardiac lesion.

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METHODS

All of the patients reported in this study were hospitalized in the Haynes Memorial Hospital because they had whooping cough. The diagnosis was proved in each instance on the basis of (1) typical catarrhal phase followed after seven to fourteen days by paroxysmal coughing, often accompanied by a characteristic whoop, (2) the presence of leukocytosis in the peripheral blood with an appreciable relative increase in lymphocytes significant for the age of the patient, and (3) isolation of *Hemophilus pertussis* from nasopharyngeal cultures. No chemotherapeutic agents were administered. Treatment consisted essentially of careful maintenance of fluid and electrolyte balance as determined by frequent chemical study of the blood, and refeeding when the patients vomited. The average duration of stay in the hospital was about two weeks; all of the patients showed a gain in weight at the time of discharge. Human hyperimmune pertussis serum was administered to all of the children 2

years of age and younger; 20 ml. was given intramuscularly every forty-eight hours for three doses.

Electrocardiograms (12 leads) were taken of all of the patients, every other day when possible, but never less than twice a week during the entire period of hospitalization. Cases complicated by any type of secondary bacterial infection were omitted from the study. The tables of Ashman and Hull[8] were used for reference in interpreting the significance of conduction time in relation to age and cardiac rate.

RESULTS

A total of fifty-one patients were studied. The numbers of males and females were approximately equal. The age distribution of the group was as follows: 1 to 6 months, sixteen; 6 to 24 months, sixteen; 2 to 5 years, ten; 5 to 10 years, eight; and age 25, one case.

In all, 325 electrocardiograms were obtained, an average of a little over six tracings per case. Physical examination of the heart was carried out daily and a number of six-feet chest x-rays were made; in no instance was physical or roentgenographic evidence of cardiac disease detected. No significant electrocardiographic changes which could be attributed to pertussis were observed. Three patients showed a more vertical position of the heart with clockwise rotation during the acute phase of the whooping cough than was noted later during convalescence. Two children were found to have persistently longer P-R intervals (no greater than 0.025 second) than the upper limit of normal established for their age and cardiac rate by Ashman and Hull.[8] Since the conduction time did not shorten before the patients were discharged from the hospital, this change could not be attributed, with any confidence, to pertussis.

DISCUSSION

The study reported in this paper indicates that pertussis does not produce significant cardiac damage as reflected by electrocardiographic abnormalities during the paroxysmal or convalescent stages of the disease. Although the so-called "catarrhal" phase of whooping cough is the period during which, on the basis of the number of patients from whose respiratory tracts the causative organisms can be isolated, the greatest impact of the infection on the heart might be expected, there are unfortunately no data concerning electrocardiographic findings during this stage.

In all cases of pertussis in which abnormal tracings are obtained, the possibility of secondary bacterial infection must be considered because of the documented appearance of abnormal electrocardiograms in a variety of viral and bacterial diseases.[9] Furthermore, in addition to myocarditis, the occurrence of bacteremia may lead to the development of pyogenic complications, such as endocarditis or pericarditis. It has been suggested that *H. pertussis* produces an "angiotoxin" which affects the endothelium of blood vessels. There is no evidence, however, that this substance affects the cardiovascular system to a clinically significant degree.

Malnutrition and electrolyte imbalance may produce electrocardiographic abnormalities. These factors were not present in the cases reported in this paper, since all of the children

had normal electrolyte balance as determined by chemical study, and gained weight.

The three patients in this study who were found to have a more vertical heart position with clockwise rotation during the height of the disease and not during the period of convalescence conceivably could represent instances of right ventricular dilatation. The changes were not striking, however. An equally plausible explanation for the change might be the fact that depression of the diaphragms from pulmonary emphysema, a not rare finding in severe pertussis, produced a shift in the electrical position of the heart. Pneumonia or atelectasis, either of which may induce strain of the right ventricle, was not present in any of the patients during the period of the study.

CONCLUSIONS

1. Uncomplicated pertussis is not accompanied by demonstrable significant electrocardiographic abnormalities or physical evidence of cardiac damage during the paroxysmal or convalescent stages of the disease.

2. Observed cardiovascular changes may be related to secondary bacterial infections or atelectasis, not uncommon complications of pertussis.

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EXCHANGE TRANSFUSION USING HEPARINIZED BLOOD

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THIS is a preliminary report of what seems to us to be an improvement in exchange transfusion technique. We shall describe the first twenty-seven exchange transfusions done in the Department of Pediatrics at Sacred Heart General Hospital using heparinized blood.

Ideally, cord blood should be obtained at the time of delivery of any infant in whom difficulty is anticipated. Our indications for exchange transfusion include evidence of sensitization with a cord hemoglobin below 15 grams per cent. Evidence of sensitization may be obtained by determining maternal antibodies prior to delivery or by a positive direct Coombs test on the cord blood. However, the incidence and severity of erythroblastosis are not well correlated with the maternal titer. Another important indication is a history of erythroblastosis in previous pregnancies. Although the maternal liver is effective in eliminating the excess bilirubin, if a cord bilirubin determination is over 3 mg. per cent an exchange transfusion should be performed. An infant whose bilirubin rises above 20 mg. per cent should have an exchange transfusion. When signs of immaturity or signs of erythroblastosis are manifest on examination, we are more likely to do an exchange. The effects of exchange transfusion are definite. If cardiac failure is present, definite improvement follows. The hemolytic rate is slowed, anemia is corrected, and much of the circulating bilirubin and antibodies are removed. It has been our practice to do re-exchanges as often as necessary to keep the bilirubin below 20 mg. per cent. Our technique resembles that described by Diamond and associates,[2] with one striking exception. We use freshly drawn, type-specific, Rh-negative, heparinized blood.

A search of the literature reveals infrequent reference to the use of heparin. Gaffney[3] states that heparinization of the infant as described by Wiener and Wexler[4] should be avoided because severe hemolytic disease often has a hemorrhagic component. Frequent rinsing of the syringe with heparinized physiologic saline solution is described in the seventh M & R report on erythroblastosis fetalis.

There are several reasons why the use of fresh heparinized blood might be considered advantageous. First, the blood does not have a chance to cool, since it is used within a few hours after being drawn and is not refrigerated prior to the exchange transfusion. The danger of introducing cold blood into the heart has been referred to in a previous paper.[5] Another advantage is the absence of any diluting fluid such as the ACD fluid that was previously used in citrated

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blood exchange transfusion. That cardiac complications may develop from a toxic level of citrate in the blood alone was also referred to in the previous paper.[5] Furthermore, the use of heparinized blood makes frequent injection of calcium gluconate unnecessary, since there are no problems with tetany. The danger of increased potassium from breakdown of cells is, of course, eliminated with the use of fresh blood. The procedure itself is technically much simpler, since there is no clotting of blood on introduction or withdrawal; in fact, the whole procedure may often be done using only one syringe. Furthermore, careful observations by the anesthesiologists who have helped us with these procedures before and since the use of heparinized blood have indicated that the babies are not experiencing as much distress or irregularity of the pulse and respiration as previously noted. The sudden changes in cardiac rate do not occur. However, the use of heparinized blood does require a list of donors readily available. Following the advice of Ziegler,[6] we have used the standard Baxter plasma vacuum bottle into which is introduced 50 mg. of intravenous heparin solution. The blood then can be collected by making use of the vacuum in the usual way, or the vacuum can be released through a sterile glass and cotton air filter and the blood then collected by gravity. It is necessary that the bottle be rotated during collection so as to secure thorough mixing or one may get coagulation in parts of the specimen. Although 50 mg. of heparin will keep the blood in a fluid state for at least five days, it has been our practice to use the blood within an hour or so after it is drawn, primarily because of the advantage of uncooled blood. Initial laboratory findings in fourteen infants in whom twenty-seven exchange transfusions were done using heparinized blood are shown in Table I. In only one instance was any significant effect noted during or following the exchange transfusion. In this case the infant had an episode of cyanosis and grunting respirations at the end of the procedure with râles audible over the lungs, which was interpreted as pulmonary edema which cleared quickly with oxygen administration.

The fact that these infants do so well is also a result of the general pediatric care they receive. For example, it is important to maintain the baby's temperature during and after the procedure. It has been our custom to have an anesthesiologist in attendance watching the temperature, pulse, and respiration and administering oxygen periodically. Continuous precordial auscultation is continued throughout the procedure. Since some of these babies vomit, the anesthesiologist is also available to aspirate the material, preventing difficulty in that respect. The transfusions are usually done in 20 c.c. increments with occasional venous pressure determinations. The amount of blood used is approximately 500 c.c., which is about double the infant's blood volume. Penicillin or other antibiotics are usually introduced at the time of the procedure and frequently the infants are kept on antibiotics for several days after the procedure. It has been our practice to introduce 25 mg. of protamine solution via the umbilical catheter at

the end of the procedure in an effort to reduce any hemorrhagic tendency due to the heparin. We have not seen any unusual tendency to bleed following these procedures. Careful follow the infant's course. Follow-up even after discharge from the hospital is important, since many of these youngsters require small transfusions for the correction of anemia.

TABLE I. INITIAL LABORATORY FINDINGS

CASE NO.	HEMOGLOBIN (IN GM. %)	NUCLEATED RBC/100 WBC	TYPE	RH	DIRECT COOMBS	TOTAL BILIRUBIN (IN MG. %)	NO. EXCHANGES WITH HEPARINIZED BLOOD	COMMENTS
94074	11.5	0	A	+	–	32.5	1	Third child, Rh-negative mother, jaundice at birth, first exchange with citrated blood in home hospital
93180	11.8	2	A	–	–	36.4	2	Third child, no previous Hx, apparently ABO incompatibility, temporary pulmonary edema with second exchange
91715	14.0	0	B	–	±	27.8	1	Probable ABO?
91039	11.2	26	O	+	+	16.4	1	
91600	11.0	3	A	+	–	33.9	2	Rh-negative mother, second baby had exchange, third normal, titer to 1:32, two exchanges
90721	9.8	6	A	+	+	36.0	2	
87045	14.4	7	O	+	– (indirect pos.)	16.48	1	First exchange with citrated blood, second with heparinized
87527	12.2	28	O	+	+	14.2	4	
87788	15.4	8	A	+	–	25.6	1	Rh-negative mother, third child, no previous Hx
94526	7.4	162	O	+	+	16.4	2	Second child, Rh-negative mother, antibodies 3 wk. before section, one exchange citrated, two heparinized
92120	9.8	500	A	–	+	24.3		Direct bilirubin 17.75 mg. %
96171	13.2	1	A	+	+	29.0	2	
95864	9.6	73	O	+	+	14.0	3	Last baby died of erythroblastosis fetalis
96283	15.4	15	A	+	+	14.72	3	Last baby jaundiced

hemostasis of the umbilical stump is usually obtained by a silk suture. The serum bilirubin determination is repeated as often as is necessary to fol-

SUMMARY

1. A preliminary report of twenty-seven exchange transfusions using heparinized blood is given.

2. The clinical impression that exchange transfusions with heparinized blood are better tolerated with fewer complications is described.

3. It is concluded that this improvement merits further evaluation.

I wish to thank Drs. M. B. Berryhill, B. J. Hoeflich, R. M. Overstreet, Margaret Tingle, and R. E. Turner of the Department of Pediatrics for permission to use their cases; Drs. E. D. Furrer, K. D. McMilan, and M. M. Patton of the Department of Pathology for their assistance in setting up the heparinized blood program; and Drs. C. W. Fluke, T. F. Brinton, J. A. Siebs, and D. M. Brinton of the Department of Anesthesiology for their assistance in performing the exchange transfusions.

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Flu in New England in 1647

Gods rods are teaching, our epidemical sicknesse of colds doth rightly by a divine hand tell the churches what our epidemical special disease is. Lord help us to see it, & to have such colds in the height of the heat of summer, shews us that in the height of the means of grace, peace, liberty of ordinances &c. yet may we then fall into malignant & mortal colds, apostacys, & coolings, &c. This visitation of God was exceeding strange, it was suddaine, & generall: as if the Lord had immediately sent forth an angel, not with a sword to kill, but with a rod to chastise; & he smote all, good & bad, old & young, or as if there were a generall infection of the air; which went first North to South by degrees infecting all, yea such as were on the seas neere our Coasts were so infected, & smitten: And this is remarkable, that though few dyed yet some did; and generally those that dyed were our choysest flowers, and most precious saints, . . .

REV. JOHN ELIOT'S RECORDS OF THE FIRST CHURCH IN ROXBURY, MASS.

THE CHANGING PATTERN OF RHEUMATIC HEART DISEASE

The Experience in New York City Department of Health Cardiac Consultation Clinics, 1943 to 1953

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THERE is much evidence to suggest that there has been a decline in the occurrence of rheumatic heart disease. This is particularly apparent from studies of the prevalence of rheumatic heart disease in school children. A number of studies by different investigators indicate a fall in the rate per 1,000 children, shown in Table I.

Wheatley[11] has shown that the frequency of valvular heart disease in young men in World War I was about twice the rate among those examined in World War II, and the occurrence of cardiac hypertrophy was even greater. The decrease in prevalence noted above refers to results obtained from various sources and under different geographic and socioeconomic conditions.

In addition to the studies relating to diminishing prevalence of heart disease there are numerous statements regarding the reduced severity of rheumatic fever. This was the opinion expressed in the tenth review of the American and English literature.[12] The disease studied by Bland and Jones[13] had a greater frequency of severe manifestations twenty years ago than the rheumatic fever of today. And it seems that the picture has changed since 1940 when Wilson wrote, in her book on rheumatic fever,[11] "An analysis was made of the records of 325 patients who were under observation either before or within one year after the onset. It was found that cardiac involvement had been recognized within the year of onset of rheumatic fever or in the same year in 85 per cent of the cases, an observation which supports the belief that the heart is probably always involved at the onset of rheumatic fever." This bleak statement is contrasted with the brighter one of Stollerman[15] fifteen years later: "About two-thirds of the patients treated at Irvington House recover from an initial attack of rheumatic fever without evident cardiac damage." Such observations reflect a change in the natural history of the disease.

Studies have also shown a decreasing mortality rate both in rheumatic fever and in rheumatic heart disease. Ash[16] in a fifteen- to twenty-year follow-up study reported a decrease in both the prevalence of rheumatic heart disease and the number of deaths. Wheatley's[11] studies show a decline in deaths from rheumatic heart disease of about 80 per cent since 1920 among white industrial insurance policyholders from 5 to 24 years of age. This was

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over a period of twenty-seven years. More recently an extensive study by Wolff[17] of the death toll from rheumatic fever pointed out the improved outlook. Wallace and Rich[18] investigated the mortality rate in rheumatic fever and rheumatic heart disease in New York City from 1940 through 1950. In this eleven-year period there has been a 74 per cent decrease in mortality due to rheumatic fever and an 82 per cent decrease in mortality due to rheumatic heart disease for all children under 20 years of age.

The reduction in prevalence and mortality of rheumatic heart disease described above is not only of clinical and epidemiological significance but also of administrative importance in relation to the need for hospitalization and to the types of cases referred for diagnostic consultation. Considerable data on the latter aspect have been accumulated by the Cardiac Consultation Service of the New York City Department of Health from 1943 through 1953. These have been analyzed in the present study, and are described in some detail because of their relation to the decline in rheumatic heart disease. A decrease in prevalence of rheumatic heart disease was expected to be reflected in a reduction in the number of cases of rheumatic heart disease observed in the consultation clinics and, indeed, evidence of such a reduction was noted by Wallace and Rich[18] in a comparative study of patients examined in 1943 and in 1952.

The Cardiac Consultation Service[19] was established in 1939 to meet certain deficiencies in the care of school children in whom cardiac disease was suspected. In addition, it was the plan that such a service would bring to the school physician recent knowledge of heart disease in children, offer expert cardiac diagnostic facilities to school and private physicians, and direct young "cardiac suspects" not under medical care to a proper source for competent follow-up. Diagnostic clinics were started in each of the five boroughs: The Bronx, Manhattan, Queens, Brooklyn, and Richmond. One of us (L. K.) has been cardiologist for the Brooklyn clinic since its inception.

TABLE I

YEAR	CITY	AUTHOR	NUMBER OF CHILDREN	AGE (YEARS)	RATE PER 1,000
1921	New York	Halsey[1]	44,000	6-16	4.3
1927	Boston	Robey[2]	119,337	6-15	4.5
1937	Philadelphia	Cahan[3]	33,293	6-14	5.0
1938	San Francisco	Sampson[4]	13,338	5-19	2.2
1939	Cincinnati	Rauh[5]	85,389	5-19	2.0
1941	Louisville	Weiss[6]	41,905	6-15	3.6
1946	Washington, Iowa	Jackson[7]	5,058	5-19	2.7
1948	San Francisco	Robinson[8]	57,768	5-18	2.4
1951	Toronto	Gardiner[9]	74,450	5-15	1.6
1953	Buffalo	Mattison[10]	71,107	6-14	1.8

Each clinic is manned by a supervising cardiologist and examining cardiologists. In addition, each clinic has a clinical assistant, a laboratory technician, and a part-time public health nurse.

Referrals are received from child health stations, elementary and high schools, mercantile working paper clinics, private physicians, and, on occasion, from hospital clinics and com-

munity welfare agencies. Although patients are accepted up to 20 years of age, referral beyond high school age is most unusual.

At the first visit, a routine blood sedimentation rate test and conventional limb lead electrocardiogram are taken in the laboratory. This is followed by a history, physical examination, and fluoroscopy before and after a barium swallow. Additional laboratory tests are available for the cardiologist, such as precordial electrocardiograms, urinalysis, complete blood count, and a sickle-cell determination.

This is a one-visit consultation service and re-examinations are not the rule. However, a re-examination appointment may be made at the request of the cardiologist or the referring physician or clinic. Although, in the past, re-examinations were performed in many instances over a period of many years in the attempt to establish a precise diagnosis, now there is an effort on the part of the clinics not to extend the re-examination period for more than two years.

The history, physical examination, and diagnosis are recorded on charts which embody many of the details of the New York Heart Association records. Diagnoses are used in accordance with the recommendations in the *Nomenclature and Criteria for Diagnoses of Diseases of the Heart*[20] although charts will be changed shortly to incorporate the newly revised nomenclature.[21] In order to establish a positive diagnosis of rheumatic fever, great emphasis was placed on a history of illness where the patient was bedridden for many weeks or months and more particularly where the patient was observed in a hospital and subsequently had convalescent care over a long period.

TABLE II. ANNUAL NUMBER OF EXAMINATIONS MADE IN CARDIAC CONSULTATION SERVICE CLINICS, NEW YORK CITY, 1943 TO 1953

YEAR	TOTAL	FIRST EXAMINATION		RE-EXAMINATION	
		NUMBER	PER CENT	NUMBER	PER CENT
1943	4,260	3,809	89.4	451	10.6
1944	4,674	3,912	83.7	762	16.3
1945	4,509	3,919	87.0	590	13.0
1946	5,363	4,710	87.8	653	12.2
1947	5,752	4,878	84.8	874	15.2
1948	6,365	5,354	84.3	1,011	15.7
1949	6,888	5,248	76.2	1,640	23.8
1950	7,084	5,253	74.2	1,831	25.7
1951	7,678	5,584	72.7	2,094	27.3
1952	6,931	4,942	71.3	1,989	28.7
1953	5,540	4,217	76.1	1,323	23.9
Total	65,044	51,826	79.7	13,218	20.3

RESULTS

The data available for analysis in the present study were the annual summaries of the number of cases examined in each clinic and their diagnostic classification. A tabulation of the annual number of cases examined from 1943 to 1953, inclusive, is given in Table II, indicating those seen for the first time and those referred for re-examination. The number of children seen each year rose from 4,260 in 1943 to 7,678 in 1951, and then declined to 5,540 in 1953. During the eleven-year period under consideration a total of 65,044 exam-

inations were made. Of these, about 80 per cent were first examinations and 20 per cent re-examinations. The percentage of re-examinations rose from 14 per cent before 1949 to 26 per cent since 1949.

A preliminary study was made of the effect of re-examination on the diagnostic pattern of patients seen in the clinics. According to a random sample of two hundred cases, comprising 2 per cent of the re-examined group, the number of examinations made varied from two to six per person, with an average of 2.8 visits over a period of several years. Based on the total clinic register, fewer than 3 per cent of the referrals in a given year were re-examined in the same calendar year. About 40 per cent of those re-examined had originally been classified as "possible heart disease," and the remaining 60 per cent were evenly distributed among the other types of cases, viz. noncardiac, potential heart disease, rheumatic heart disease, and congenital heart disease. Re-examination reduced the percentage of cases with possible heart disease, and increased those considered as noncardiac. The proportionate distribution of all other groups, representing those with organic heart disease or a history of rheumatic fever, did not appear to be significantly affected by re-examination.

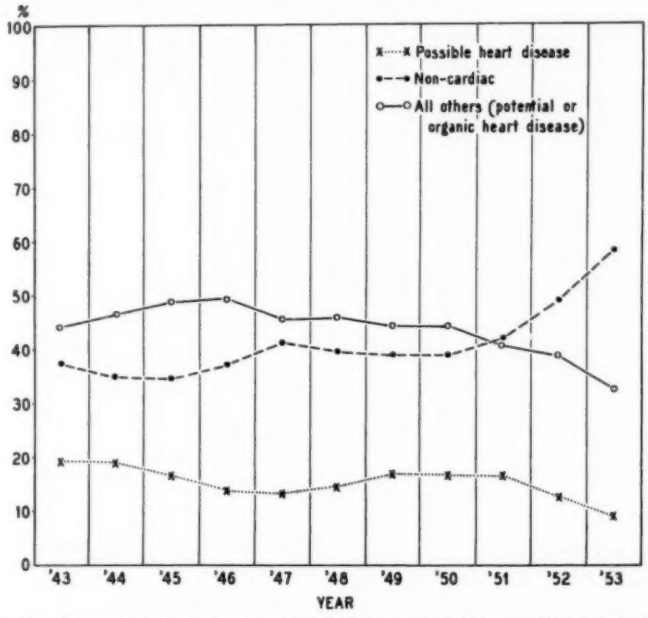

Fig. 1.—Relative frequency of diagnoses classified as noncardiac, possible heart disease, and all others, New York City, 1943 to 1953.

Because of these varying effects of re-examination, the cases observed in the clinic each year were preliminarily subdivided into three groups, the noncardiac, possible heart disease, and all others, representing those with organic heart disease or a history of

rheumatic fever. The annual percentage distribution of all the patients seen in the clinics, by these three broad groupings, is shown in Fig. 1. The trend in each group showed little, if any, change until 1951. After that, there was a rise in the percentage of noncardiacs and a coincidental fall in the other two groups. These deviations from the horizontal trend in recent years seem to be related partly to an increase in the percentage of reexaminations and partly to the types of patients initially referred to the clinics. The rise in proportion of reexaminations tended to increase the percentage of noncardiacs and decrease the proportion of possible heart disease, as noted above. The influence of possible changes in type of clinical referral cannot be precisely determined from the data available. However, further examination of the group with organic or potential heart disease revealed evidence of a change in the pattern of referrals which appeared to be of epidemiological significance.

The individuals with organic or potential heart disease were considered under four broad diagnostic classifications, of which three were related to rheumatic fever either clinically or historically, as follows: history positive and heart signs negative (potential heart disease); history positive and heart signs positive (rheumatic heart disease); history negative and heart signs positive (unknown heart disease, rheumatic type). The fourth group consisted of those with congenital heart disease. The relative frequency of these four types of patients, by calendar year, is shown in

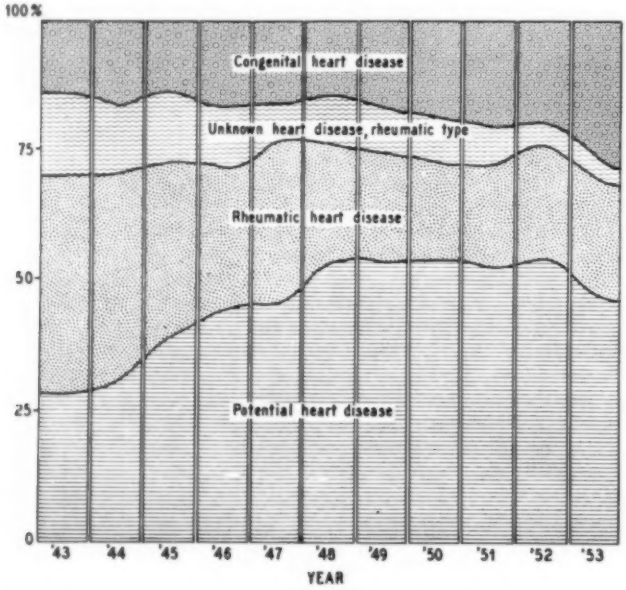

Fig. 2.—Cumulative percentage distribution of patients with potential or organic heart disease, New York City, 1943 to 1953.

Fig. 2. There were pronounced changes in the relative frequency of the three groups related to rheumatic fever. From 1943 to 1948, the percentage of individuals with potential heart disease increased sharply, while those with rheumatic heart disease decreased sharply. These changes balanced out, so that the cumulative frequency of the groups related to rheumatic fever showed little fluctuation, varying from 83 to 86 per cent of the total number. After 1948, however, their combined percentage declined to about 74 per cent in 1953. The drop in percentage of individuals whose findings were related to rheumatic fever was accompanied by a progressive increase in the relative size of the group with congenital heart disease, which rose from 17 per cent in 1949 to 26 per cent in 1953.

The changes in trend occurring in the rheumatic fever group may be more clearly seen in Fig. 3 showing the relative frequency of organic heart disease among those referred to the various clinics with a history of rheumatic fever. The proportion of children with detectable heart disease decreased from 60 per cent in 1943 to 30 per cent in 1948, and then remained at about this level between 1948 and 1953. A fall in the relative frequency of heart disease following a history of rheumatic fever was observed in every clinic, with one possible exception where the changes were not considered statistically significant. In two clinics (Tremont and Lower East Side) comprising 47 per cent of the total examined, the percentage of cases with cardiac complications reached low levels of 20

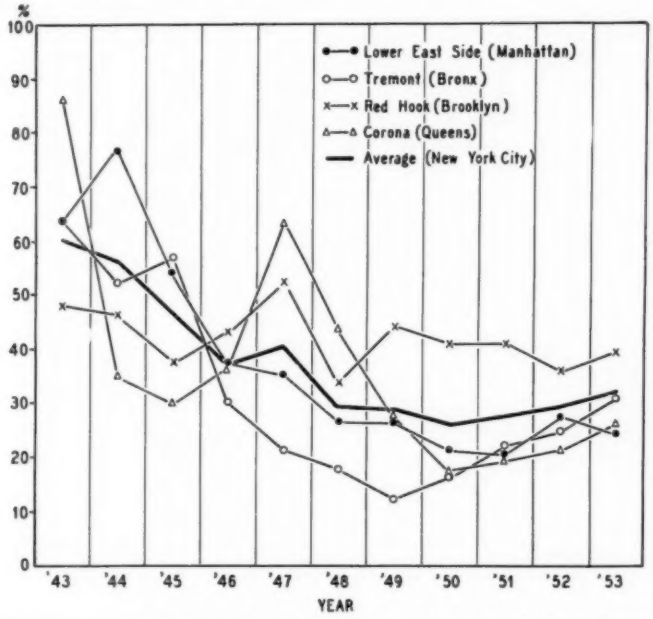

Fig. 3.—Relative frequency of organic heart disease in patients with history of rheumatic fever, by Cardiac Consultation Service Clinic, New York City, 1943 to 1953.

and 25 per cent, respectively, from 1948 through 1953. The low percentage of referrals with organic heart disease is consistent with the reduction in prevalence of rheumatic heart disease reported by various investigators.

It is of interest to note that 86 per cent of the patients with a history of rheumatic fever had been referred to the clinic following the first attack, and 14 per cent after two to five attacks, according to a review of 200 cases chosen at random and representing a 1 per cent sample of the group with a history of rheumatic fever. The frequency of detectable heart disease was about 35 per cent higher in those with a history of more than one attack of rheumatic fever than those with only one known attack.

The sample studied also revealed that the time interval elapsing between the onset of the first attack and the date of examination at the clinic varied widely, from less than one year to fifteen years, with an average of 5.8 years. A summary of the distribution of referrals in the sample studied, by time interval between the first rheumatic fever attack and examination in clinic, follows:

Interval (Years)	*Number*	*Per cent*
0-4	102	51.0
5-9	68	34.0
10-14	28	14.0
15-19	2	1.0
Total	200	100.0

About half the children were referred less than five years after the first attack. This group included 11 per cent examined less than one year and 26 per cent less than two years after the first attack. Thus, about 75 per cent of the children referred to the clinic with a history of rheumatic fever were seen two or more years after their first attack. The time that elapsed between the onset of rheumatic fever and clinic examination was comparable for those with and without organic heart disease.

DISCUSSION

In the present study, clinical data accumulated by the Cardiac Consultation Clinics of the New York City Health Department from 1943 to 1953, inclusive, were analyzed in relation to the occurrence of organic heart disease following rheumatic fever. These clinics serve as diagnostic centers for the general population of children under 21 years of age in whom heart disease is suspected because of a history of rheumatic fever or because of symptoms or signs attributed to the heart. They obviously represent only a part of the total community of children with heart disease or history of rheumatic fever. Consequently, specific incidence rates could not be calculated. Furthermore, since the number of children examined each year was partly limited by administrative factors, absolute numbers were not useful in studying trends. Consequently, relative frequencies were used as the basis for comparison between one year and another.

The validity of the data used in the investigation may be questioned on at least two grounds, the accuracy of diagnosis, and bias in types of cases referred to the clinics for examination. These difficulties are regularly encountered in retrospective studies based on case records of clinic or hospital data. They were seriously considered in the evaluation of the data collected and in the decision to publish the results obtained. With respect to the accuracy of diagnosis, the

study was aided by the criteria established by the New York Heart Association. These served as the basis for clinical diagnosis throughout the study period. The quality of examination was maintained by the use of Board-qualified physicians or Board members in pediatrics and internal medicine, by the application of various laboratory tests as noted above, and by the limitation in the number of cases examined per clinic session. Only during the war years of 1942 to 1945 was it difficult to maintain personnel standards.

The types of cases referred were determined in part by administrative policy and in part by the source of referral. Clinic policy was fixed at the start of the program and remained unchanged. All children referred by physicians were acceptable. Appointments were made in the order in which they were requested, and were limited only by lack of personnel. There was thus no evidence of selection of specific types of cases by the clinics. However, there was no way of regulating the type of case referred by the physician. This depended not only on the value attached by the physician to the clinic services rendered but also on innumerable factors affecting the use of an available community resource. For example, the development of cardiac surgery may have led to proportionately more referrals with organic heart disease, especially congenital defects. The increased emphasis on rheumatic fever programs and the control of rheumatic fever may have altered the number of referrals with and without cardiac disease.[22] The extent to which these variables modified the trend in the results observed in the clinics is unknown. They point up the need for long-term studies of total population groups in measuring changes in the natural history of rheumatic fever.

Although it is difficult to interpret the data examined, because of the shortcomings noted above, certain associations were observed which may be of epidemiological significance. A decline in the relative frequency of organic heart disease following rheumatic fever was observed in every clinic throughout the city. The decrease was noted between 1943 and 1948, following the extensive use of sulfonamides and paralleling the introduction of penicillin. Many factors are presumably involved, because a reduction in rheumatic heart disease antedated the use of chemotherapy by many years.

The results observed in the cardiac consultation clinics of New York City were highly encouraging, since about 70 per cent of the school children referred after 1947 with a history of rheumatic fever had no detectable heart lesions. In one area (Tremont Cardiac Clinic), about 80 per cent of those with rheumatic fever history were found to be free of demonstrable organic heart disease. These findings are related in time to the widespread use of antibiotics, and represent supportive data on the changing pattern of rheumatic heart disease.

SUMMARY

1. An analysis was made of the clinical diagnoses of 65,044 examinations by the Cardiac Consultation Service Clinics of the New York City Health Department from 1943 to 1953, inclusive, in order to determine whether there has been a change in the relative frequency of organic heart disease following rheumatic fever.

2. The relative frequency of detectable heart disease following a history of rheumatic fever in children referred to the consultation service decreased from about 60 per cent in 1943 to about 30 per cent in 1948. The 30 per cent frequency level has been maintained since 1948.

3. The foregoing findings are consistent with the decrease in prevalence of rheumatic heart disease reported from other source material by various investigators.

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BRONCHIAL ADENOMA OCCURRING IN CHILDHOOD

A Report of Three Cases

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BRONCHIAL adenoma is a rare lesion in childhood. Only ten cases have been reported previously.[1, 2] We felt it would be of value to review our experience with three cases encountered in the past three years.

CASE REPORT

Case 1.—E. F., a 9-year-old white girl, was well until seven months prior to admission, at which time she developed a cough. This responded to treatment, only to recur two months later. Because of persistent symptoms a chest x-ray was taken which demonstrated partial atelectasis of the left upper lobe. Subsequent bronchoscopy failed to reveal any abnormalities. The persistent cough and x-ray lesion led to admission to Children's Hospital of Pittsburgh on March 21, 1955.

The past history was noncontributory except for bronchopneumonia with uneventful recovery at age 6.

Physical examination and laboratory studies were essentially normal. X-rays (Fig. 1) and fluoroscopy confirmed the presence of partial atelectasis of the left upper lobe. Bronchoscopy revealed a fungating lesion protruding from the left upper lobe orifice. Multiple biopsies were taken. Although the cellular architecture suggested bronchial adenoma the tissue was too necrotic for definitive diagnosis. A bronchogram was done. The failure of the left upper lobe bronchus to fill was attributed to the tumor seen endoscopically. In an attempt to obtain a definite tissue diagnosis, the bronchoscopy was repeated. Again the multiple biopsies were too necrotic to permit accurate evaluation.

The endoscopic findings and x-ray evidence of atelectasis made exploratory thoracotomy mandatory. It was felt that the left upper lobe had been irreparably damaged. Accordingly a lobectomy was done as a biopsy and possible definitive therapy. Frozen section demonstrated a bronchial adenoma which extended to the line of transection of the bronchus. Since there was no evidence of mediastinal extension or metastases and the lower lobe was normal according to x-ray and by palpation, a sleeve resection of the main-stem bronchus was done, including the left upper lobe orifice. Bronchial continuity was established by end-to-end anastomosis. Frozen section of the resected segment was negative for residual tumor.

The postoperative course was uneventful. An adequate airway was demonstrated by bronchogram (Fig. 2). At the present time, one year later, the patient is well.

Gross Pathology.—The specimen consisted of a left upper lobe weighing 106 grams. The bronchus was occluded by a wide-based polypoid mass (Fig. 3), measuring 7 mm. at its point of attachment. The tumor was firm, lobulated, and hyperemic. On cut section the lesion was flat, pale yellow, firm, and extended down to, but

From the Departments of Pathology and Thoracic Surgery, Children's Hospital of Pittsburgh and the School of Medicine, University of Pittsburgh.

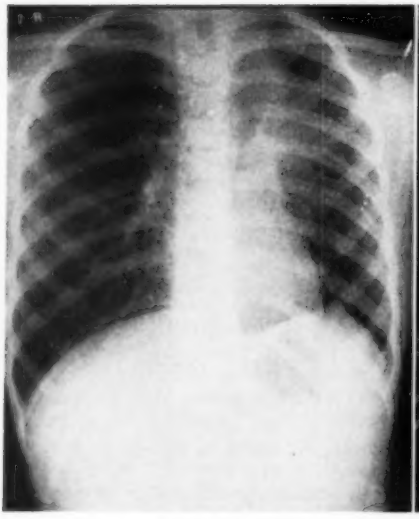

Fig. 1.

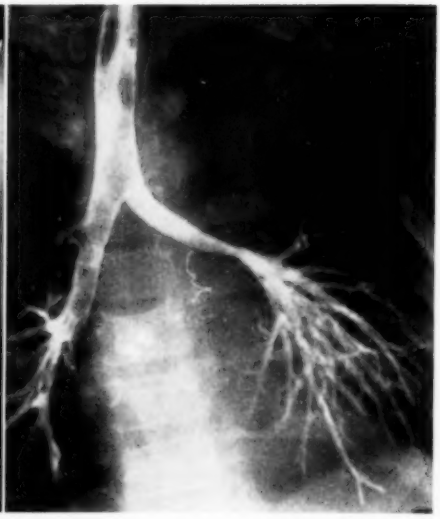

Fig. 2.

Fig. 1.—Roentgenogram of chest, Case 1, reveals left upper lobe density due to atelectasis, mediastinal shift to that side, and "tenting" of the left leaf of the diaphragm.

Fig. 2.—This postoperative bronchogram reveals continuity of the main-stem bronchus, following segmental resection and left upper lobectomy.

Fig. 3.—The darker polypoid tumor extending to the line of excision stands out on the paler bronchial mucosa of the opened main bronchus to the left upper lobe.

not beyond, the cartilaginous rings. The line of resection was at the proximal edge of the tumor. The adjacent intrapulmonary lymph nodes were slightly enlarged, uniformly soft, pale gray, and bulged on section.

No gross evidence of tumor was evident in the resected segment of main-stem bronchus.

Microscopic Pathology.—The tumor was the carcinoid type of bronchial adenoma (Fig. 4). The surface of the

Fig. 4.

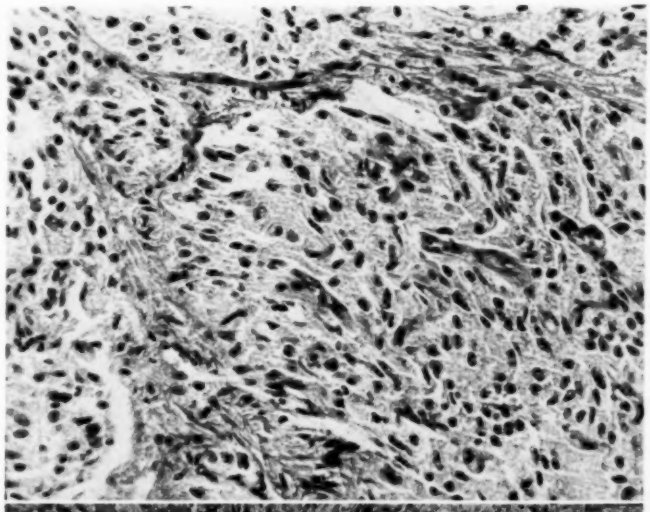

Fig. 5.

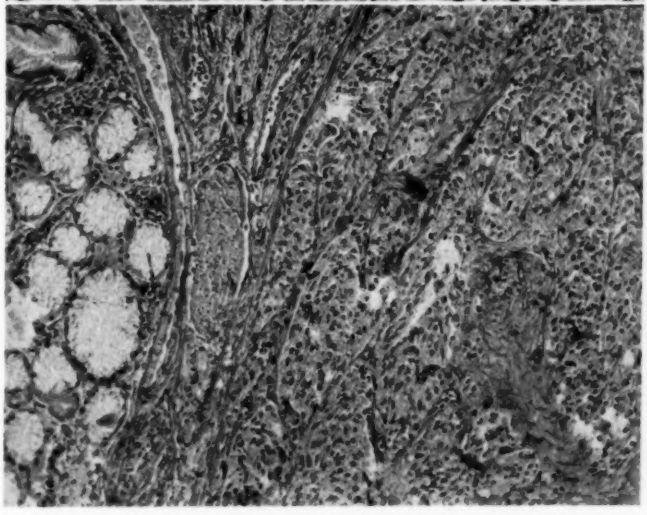

Fig. 4.—Photomicrograph of Case 1 demonstrates the compressed serous cells of the tumor in their scanty vascular stroma. (Hematoxylin and eosin; ×480; reduced ⅙.)

Fig. 5.—Photomicrograph of Case 1 shows mucus-distended bronchial glands on the left of the illustration. The adjacent tumor, composed of serous cells in carcinoid arrangement, lies to the right. (Hematoxylin and eosin; ×140; reduced ⅙.)

lesion was markedly necrotic, explaining the difficulty in obtaining a positive endoscopic biopsy. Adjacent to this necrotic area, the bronchial mucosa was altered by extensive squamous metaplasia. The base of the lesion extended to the level of the cartilaginous rings and mixed bronchial glands. A transition from mildly hyperplastic bronchial glands to tumor was observed (Fig. 5). Periodic acid-Schiff stains revealed that the red-staining mucus was confined to the bronchial glands. Only serous cells were involved in the tumor. No reticulum was present in a section stained by the Foot-Bielschowsky method.

Serial blocks through the mainstem bronchus segment failed to reveal tumor. Sections of the lymph nodes revealed no spread of tumor.

The histopathologic diagnosis was: bronchial adenoma, carcinoid variety.

CASE 2.—G. S., a 9-year-old white girl, developed a persistent cough following a tonsillectomy and adenoidectomy seven weeks prior to admission on Jan. 8, 1953. There had been no fever, chest pain, or hemoptysis. A chest x-ray revealed atelectasis of the right lower lobe (Figs. 6 and 7).

Physical examination and laboratory studies were essentially negative except for a questionable decrease in breath sounds over the right lower lobe.

Bronchoscopy revealed a smooth mass arising from the right lower lobe bronchus. It extended proximally almost to the upper lobe orifice. The middle lobe orifice was partially surrounded by tumor but was patent. A biopsy revealed only squamous metaplasia. The procedure was repeated, establishing a positive diagnosis of bronchial adenoma. Surgery was advised but was refused by the parents. Three years later the child is alive but has a persistent cough and "frequent colds."

Fig. 6. Fig. 7.

Figs. 6 and 7.—Roentgenograms of chest, Case 2, demonstrate right lower lobe atelectasis in anteroposterior and lateral projections, respectively.

Microscopic Pathology.—There was extensive squamous metaplasia of the luminal surface. The stalk consisted of masses of polyhedral cells in a cylindromatous arrangement (Fig. 8).

The cells had a granular amphophilic cytoplasm resembling the serous cells of the bronchial glands. The connective tissue stroma was more abundant than in the previous case.

The histopathologic diagnosis was: bronchial adenoma, cylindromatous variety.

CASE 3.—J. L., a 15-year-old white boy, was admitted to Children's Hospital of Pittsburgh Dec. 26, 1955, presenting a history of daily elevation of temperature beginning in April, 1955, and continuing through the month of May. Within a matter of two weeks a recurrence of fever was noted, although there were no pulmonary signs or symptoms. A chest film was taken which disclosed a marked opacity in the right lower lung field (Fig. 9). This episode of fever persisted for three weeks before responding to antibiotic therapy. On Nov. 23, 1955, a brisk pulmonary hemorrhage occurred. In mid-December elevated temperature was again present and a secondary pulmonary hemorrhage occurred. During the first two months there was a weight loss of 20 pounds, but a gain of 15 pounds was noted prior to admission to Children's Hospital.

The past medical history included measles and chicken pox in early childhood. A tonsillectomy had been carried out at the age of 6. Surgical correction of bilateral undescended testes was performed at the age of 8 years. A left inguinal hernia had been repaired when the boy was 9 years old.

Following admission, bronchoscopy disclosed a papillary lesion in the right bronchus which virtually occluded the entire lumen. A biopsy (Fig. 10) was diagnostic of adenoma of the bronchus.

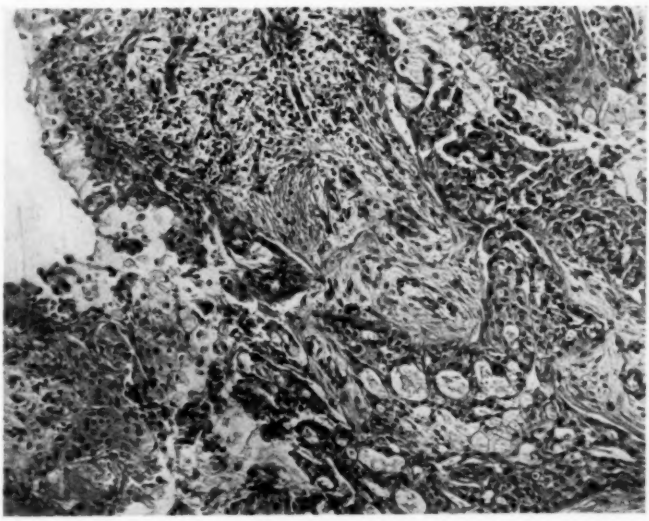

Fig. 8.—Photomicrograph, Case 2, shows the cylindromatous arrangement of the cells in their relatively abundant stroma. (Hematoxylin and eosin; ×140; reduced ⅙.)

A right total pneumonectomy was carried out on Jan. 17, 1956, and the postoperative convalescence was uneventful. The patient was discharged from the hospital eighteen days following surgery.

Gross Pathology.—The right lung and two lymph nodes, 1.5 and 0.8 cm. in maximum dimensions, were received. The lung weighed 280 grams and measured 27 by 16 by 7 cm. The

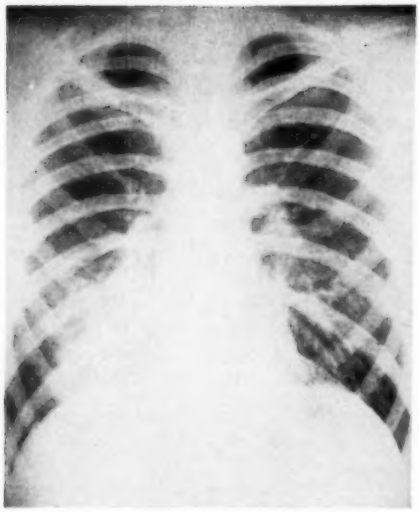

Fig. 9.—Roentgenogram of chest, Case 3, reveals right lower lobe density due to atelectasis.

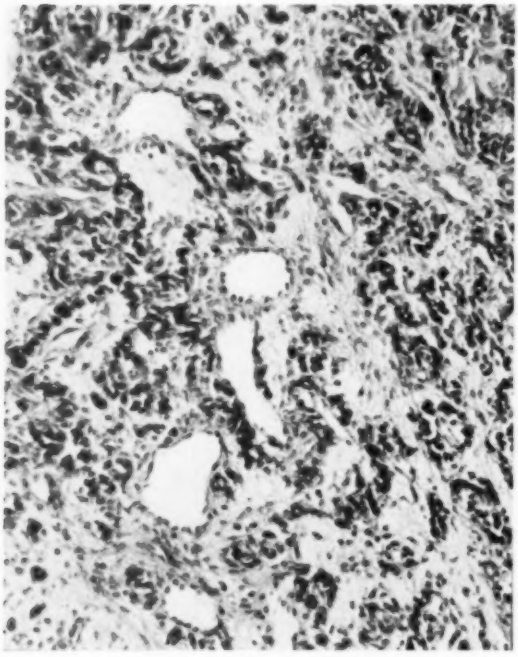

Fig. 10.

Fig. 11.

Fig. 10.—This photomicrograph of the bronchial biopsy in Case 3 is typical of that portion of the adenoma lying beneath the ulcerated surface presenting to the bronchoscopist. Structure is altered by relatively abundant edematous fibrous stroma, and compression of tumor cells, with considerable distortion and loss of cytoplasm. (Hematoxylin and eosin; ×140; reduced 1/6.)

Fig. 11.—The bronchus to the lower lobe has been opened, and the adenoma bulges from the lumen. The superior portion is ulcerated and hemorrhagic. Case 3.

Fig. 12.

Fig. 13.

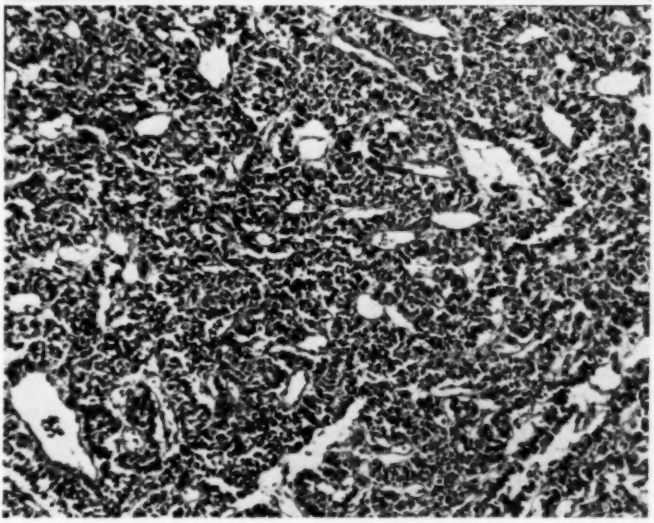

Fig. 12.—This low-power photomicrograph of Case 3 is of a section made through the broad pedicle, cut perpendicular to the bronchial wall and in its long axis. The tumor extends through the bronchial wall but is sharply circumscribed. (Hematoxylin and eosin; ×3; reduced ⅙.)

Fig. 13.—This photomicrograph of Case 3 is of a typical field in the central portion of the tumor where there is no distortion from inflammation or necrosis. Fibrous tissue is scanty and growth around the abundant vessels gives a carcinoid pattern. (Hematoxylin and eosin; ×140; reduced ⅙.)

lobes were sharply delineated and the pleura was smooth and glistening. The parenchyma was crepitant except for a dark blue, collapsed region 4 cm. across in the posterior apical segment of the lower lobe. A moderately firm polypoid mass 4.5 cm. long lay within and distended the main lower lobe bronchus. The upper extremity of the mass lay freely within the lumen and extended to within 0.5 cm. of the resected edge. This portion was ragged, ulcerated, hemorrhagic, and necrotic. Here, the mass was 1 cm. across but it quickly broadened out to 2.5 cm. at its lower extremity, where it was pale gray to pink (Fig. 11). This mass was firmly fixed to the lateral wall of the bronchus by a thick pedicle 2 cm. across. This point of attachment was just below the orifice of the superior lower lobe branch. A cut through this point of attachment revealed the bronchial wall to be absent, but the neoplasm was sharply demarcated from the adjacent lung by a thin, just visible, fibrous capsule (Fig. 12). The tumor blocked the orifices of the posterior, medial, lateral, and anterior basal bronchi. All were dilated and contained yellow mucoid or blood-tinged material. The posterior basal segment was collapsed and dark red to blue, while the remaining lung was pale gray to pink, and crepitant.

Microscopic Pathology.—Sections through the central portion of the tumor were composed of a uniform pattern of small rounded or oval cells packed between small, thin-walled vessels. The cytoplasm was scanty and granular. Cell outlines were indistinct. There were no mitotic figures (Fig. 13). Sections including the bronchial surface revealed ulceration or squamous metaplasia of the covering epithelium. The tumor close to the surface was distorted by marked increase in fibrous stroma that compressed cells, giving the pattern seen in the biopsy (Fig. 10). In sections through the base, the tumor penetrated the bronchial wall between the cartilages. The advancing edge was sharply separated from adjacent structures by a thin layer of fibrous tissue.

Sections of the two lymph nodes received with the specimen and twelve other lymph nodes removed from the lung were free of tumor.

The histopathologic diagnosis was: bronchial adenoma, carcinoid variety.

DISCUSSION

Bronchial adenoma manifests itself, clinically, primarily by cough, hemoptysis, and repeated lower respiratory tract infections. This is associated with the partial to complete bronchial obstruction accompanied by distal infection. These lesions arise primarily in the large bronchi and, therefore, are accessible for bronchoscopic biopsy. However, as in our first case, secondary infection and necrosis may make tissue diagnosis difficult.

A knowledge of the various growth patterns of bronchial adenomas is necessary for proper management of these cases. There is a low but definite incidence of metastases with these lesions. McBurney and coworkers[3] reported nine metastasizing adenomas in a series of 111 adults. In reviewing the literature they found that seventy-eight of 700 reported cases had metastasized. McBurney found that both the cylindromatous and carcinoid types may metastasize. Enterline and Schoenberg[4] believe the cylindromatous variety to be much more dangerous and anatomically sufficiently different to justify its classification as cylindromatous carcinoma. It is fair to state that bronchial adenomas grow slowly and about 10 per cent will metastasize. Patients may survive for years with proved distant metastases.[3] In

addition to the lymphatic and blood-borne metastases, adenomas are frequently locally invasive, especially to vital mediastinal structures. There is no reason to expect bronchial adenomas to display any less aggressiveness in children.

The treatment of bronchial adenoma is surgical resection by thoracotomy. Bronchoscopic removal is mentioned only to be condemned. The amount of lung to be resected must be governed by the extent of disease encountered. Whenever the lesion is favorably located, the lung function has not been destroyed by repeated infection, and extension of the tumor has not occurred, conservative resections are indicated. Frequently, however, pneumonectomy will be necessary because of the associated lung damage, as well as to ensure adequate removal of the tumor. Thomas,[5] reporting forty-one cases, found pneumonectomy necessary in twelve, although lobectomy was sufficient in twenty-two. Local excision and bronchial reconstruction was possible in five of Thomas' cases and two were not treated.

SUMMARY

Three cases of bronchial adenoma occurring in children are reported. Two were treated by resection. In the other, surgery having been refused, the patient is still alive with symptoms three years after the diagnosis was made.

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A Wise Precaution

On the night of the 10th inst. the wife of Mr Thomas Hubbard, of Brimfield, in this state [of Massachusetts], was delivered of a singular object, weighing about nine pounds.

The child was born, or rather was produced dead, having two heads and faces—two necks—four arms—four thighs and legs, and feet—but having only one trunk or body. Every part was perfect, and the child handsomely featured.

This is a singular production but it may be relied on as certain. If any dispute it, they may see it by applying at the house of Dr. Thomas Babbit, of Sturbridge, who has obtained liberty to carry it home to preserve in spirits, to gratify the curiosity of the inquisitive.

THE IMPARTIAL REGISTER, Salem, June 9, 1800.

ACCIDENTAL POISONINGS IN CHILDHOOD AND THEIR PREVENTION

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NEW YORK, N. Y.

HISTORICAL BACKGROUND

UNPRECEDENTED advances were made in recent years in science and technology. The immediate application of the new knowledge in industry accelerated an ever-increasing number of new products, drugs, and household preparations on the market and hence in the American home. This boon to progress, however, has also created problems and difficulties since these *new* preparations are also potential hazards and are responsible for the marked rise in accidental chemical poisonings.[1-3] For the purpose of this discussion a "poison" is defined in broadest terms as follows: "any substance which may cause injury or produce untoward symptoms or toxic manifestations by ingestion, absorption, or inhalation."

PATHOGENESIS AND EPIDEMIOLOGY OF ACCIDENTAL CHEMICAL POISONINGS IN CHILDREN

In order to gain further knowledge about accidental chemical poisonings (gas exempted) more accurate and precise information is needed on the epidemiology of these occurrences. Gordon[4] correctly stated that "accidents follow a basic epidemiologic pattern and must be studied in the same manner as any other disease entity." Not only the agent but also the host and the environment, biologic, cultural, and social, and their interaction must be investigated and understood before sound preventive countermeasures can be formulated.

This study was designed to obtain such information, to analyze it critically, and to suggest control measures based on the facts obtained.

This report is limited to data obtained on 646 accidental chemical poisonings in children under 16 years of age. A home visit by an experienced public health nurse in addition to the information obtained from the reporting physician and hospital was made on each case and included as an integral part of the study.

SUMMARY OF POISON CONTROL CENTER DATA

The etiology of poisonings by type of injurious agent, and age, is shown in Table I. Internal preparations were the chief offenders and were responsible for 29 per cent of all poisonings in this group. Cleaning, sanitizing, and bleaching agents came next, and "external preparations" were the third leading cause. Together, the above three groups contributed 66 per cent of all accidental poisonings.

Age.—Age 1 was the age of highest risk, accounting for 37 per cent of the total, with age 2 following closely be-

From the New York City Department of Health.

Presented before the Spring Session of the American Academy of Pediatrics, Houston, Texas, April 18, 1956.

hind and responsible for 31 per cent of poisonings. Children at these two ages, 1 and 2 years, are the most susceptible and are together responsible for 68 per cent of the total number included in this report.

The frequency of poisonings due to "internal medications" was highest at age 2 years, while poisonings from "cleaning, sanitizing, and polishing agents" took the greatest toll at age 1. This was also true of "petroleum distillates and solvents," and "insecticides."

The type of poisoning by age highlights the intimate association between an accidental poisoning and a child's stage of growth and development.[5] It is in direct proportion to the child's frequency of exposure to unsafe agents and environment. At 1 year of age the child is still crawling about and unable to climb, and thus becomes victim to substances

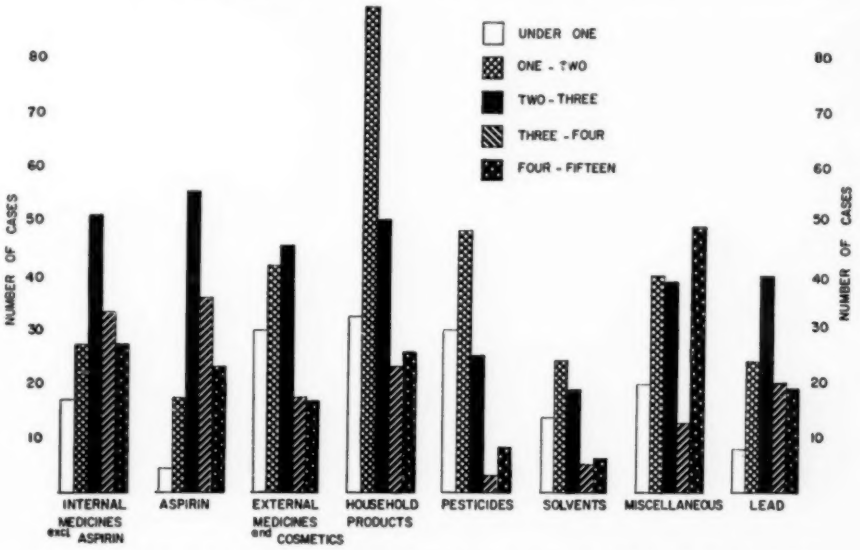

Fig. 1.—Poisonings by age and type of poison in patients under 15 years of age, 1955.

TABLE I. POISONINGS BY AGE, 1955

GENERIC CLASS	NO.	PER CENT	AGE IN YEARS					
			UNDER 1	1	2	3	4	5 AND OVER
External preparations and cosmetics	95	14	8	32	33	13	4	5
Internal preparations	191	29	7	27	79	40	21	17
Cleaning, sanitizing, and polishing agents	147	23	2	70	36	18	9	12
Petroleum distillates and solvents	58	9	1	40	8	5	1	3
Rodenticides	18	3	3	6	6	2	1	
Insecticides	55	9	3	30	17	1	1	3
Turpentine	18	3	2	8	7			1
Miscellaneous	64	10	5	24	15	7	3	10
Total	646	100	31	237	201	86	40	51
Per cent			5	37	31	13	6	8

which are readily found on the floor, under the sink, or at other similar places of low levels which he can reach. At 2 years he has greater mobility and exploration; he can reach and climb to higher levels, such as drawers, bureaus, shelves, and open cabinets.

As the child learns from experience, he becomes more cautious and discriminatory and hence a material reduction is noted in the number of poisonings, with increased age, from 37 per cent at age 1 to 6 per cent at age 4 years. The reason for the small incidence at under 1 year of age is probably greater parental supervision and protection at this young age.

Sex and Ethnic Group.—The variability with sex and ethnic group is presented in Table II. Fifty-five per cent of all poisonings reported were among males and 45 per cent in females. This proportion holds true for both whites and nonwhites, though this is not a statistically significant difference. A much higher incidence is observed for the nonwhite 34 per cent, which is more than twice their percentage composition of the general population. This observation was noted previously[5] and is undoubtedly related to socioeconomic conditions rather than to inherent differences.

Time and Place of Occurrence (Tables III and IV).—Forty-two per cent of all poisonings occurred between 12 NOON and 6:00 P.M. and an additional 36 per cent between 6:00 A.M. and 12 NOON. This reflects the time of day at which the child is up and about and at play.

The seasonal variation is not conclusive, since it may portray the increasing activity of the Poison Control Center rather than a seasonal trend.

There is a distinct correlation between poisonings and environment. The kitchen is the *most dangerous place,*

TABLE II. POISONINGS, BY SEX AND ETHNIC GROUP, 1955

	TOTAL		ETHNIC GROUP						
			WHITE		NONWHITE		PUERTO RICAN		NOT STATED
SEX	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.
Male	358	55	199	56	126	57	22	44	11
Female	288	45	159	44	94	43	28	56	7
Total	646	100	358	100	220	100	50	100	18

TABLE III. POISONINGS BY TIME OF DAY AND MONTH OF ACCIDENT, 1955

MONTH	TOTAL	6 A.M.–12 NOON	12 NOON–6 P.M.	6 P.M.–6 A.M.	NOT STATED
January	1			1	
February	0				
March	2		1	1	
April	11	1	4	3	3
May	24	7	12	5	
June	59	21	28	9	1
July	95	39	35	18	3
August	76	26	30	20	
September	72	29	26	15	2
October	91	33	43	13	2
November	102	36	42	22	2
December	113	39	51	21	2
Total	646	231	272	128	15
Per cent	100	36	42	20	2

accounting for 34 per cent of all poisonings. The bedroom contributes an additional 27 per cent, and the bathroom is responsible for 15 per cent of poisonings in children. This is also intimately linked with the child's age. More accidents in the younger ages occur in the kitchen.

Type of Supervision at Time of Accident (Table V).—In 93 per cent of instances there was an adult member of the family present in the home at the time of accident. In 76 per cent it was the mother. However, the accident occurred at a time when the adult member present was not in direct supervision, being either in a different room or out of the child's view. It is observed that most of the occurrences (68 per cent) were reported in children of the younger age group, at ages 1 and 2 years when they are still in need of parental supervision.[6] At these ages children show lack of caution and inexperience and are very susceptible and vulnerable to unsafe conditions in and about the home.

Preventability (Table VI).—Ninety-five per cent of all poisonings were definitely classified as preventable by the public health nurses visiting the homes. In 3 per cent it was not definitely stated as to whether they were preventable or not. A close scrutiny of the mode of occurrence indicates that these were definitely preventable. Only in 2 per cent were they believed to be unpreventable, i.e., suicidal attempts.

Original Container of Injurious Agent at Time of Poisoning.—Table VII shows that 70 per cent of the agents involved were in their original containers. There was a marked

TABLE IV. POISONINGS BY PLACE OF ACCIDENT, 1955

PLACE OF ACCIDENT	NUMBER	PER CENT
Kitchen	220	34
Bedroom	171	27
Bathroom	97	15
Living room	61	9
Directly outside of home*	32	5
Foyer	13	2
Cellar	9	1
Other	30	5
Not stated	13	2
Total	646	100

*This includes steps of house, front and back yards, but does not include street or street away from home.

TABLE V. POISONINGS BY TYPE OF SUPERVISION, BY AGE OF PATIENT, 1955

	TOTAL		AGE IN YEARS					
	NO.	PER CENT	UNDER 1	1	2	3	4	5 AND OVER
None	40	6	1	9	11	4	1	14
Mother	491	76	23	197	149	65	31	26
Father	19	3	2	7	7	–	–	3
Other member of family, adult	36	6	1	12	11	6	4	2
Other member of family, minor	15	2	2	2	4	5	2	–
Other, adult	32	5	2	8	14	3	2	3
Other, minor	5	1	–	1	1	–	–	3
Not stated	8	1	–	1	4	3	–	–
Total	646		31	237	201	86	40	51
Per cent		100	5	37	31	13	6	8

variation, however, by type of poison. In only 33 per cent was turpentine found to be in the original container; rodenticides followed with 44 per cent, and petroleum distillates with 45 per cent. Eighty-eight per cent of the "internal" and 83 per cent of the "external" preparations, however, were in their original containers but were unfortunately placed where they were accessible and intriguing to children, sink, or in the washtub or washing machine, ready for use. Clorox, being colorless, was ordinarily mistaken for water and ingested. The solvents, i.e., kerosene, benzene, turpentine, etc., were usually left after use in a jar, soda bottle, drinking glass, soup can, or saucer.

The misplacing of injurious agents from original containers to household utensils and their availability in open

TABLE VI. POISONINGS BY PREVENTABILITY AND OUTCOME, 1955

PREVENTABILITY AND OUTCOME	NUMBER	PER CENT
Preventable, full recovery	599	93
Preventable, injury	7	1
Preventable, fatal	4	1
Not preventable, full recovery	14	2
Not stated	22	3
Total	646	100

TABLE VII. POISONINGS BY CONTAINER AT TIME OF POISONING, 1955

GENERIC CLASS	TOTAL NO.	IN ORIGINAL CONTAINER		NOT IN ORIGINAL CONTAINER NO.	NOT STATED
		PER CENT OF TOTAL	NO.		
External preparations and cosmetics	95	83	79	14	2
Internal preparations	191	88	169	19	3
Cleaning, polishing and sanitizing agents	147	65	96	48	3
Petroleum distillates and solvents	58	45	26	32	
Rodenticides	18	44	8	9	1
Insecticides	55	58	32	23	
Turpentine	18	33	6	11	1
Miscellaneous	64	59	38	19	7
Total	646	70	454	175	17

such as on tables, floor, shelves, in drawers, open closets, on bedroom furniture, in medicine chests, or handbags. A child's normal mobility, enterprise, lust for exploration, and curiosity thus made the occurrences completely natural, though entirely preventable. The bleaches were usually not in their original containers. Drinking glasses, soda bottles, cola bottles, mayonnaise jars, saucers, glass pitchers, cups, and milk bottles were commonly used for their storage. These were frequently placed on the table or sink, under the and easily accessible places was a contributory factor in many occurrences.

Previous Accidents, Other Hazards and Influences.—Twelve per cent of the persons involved had suffered from previous accidents. In 13 per cent a familial history of an accidental occurrence was obtained. Seventeen per cent gave a history of pica. It is not definitely known whether these figures are higher than for the general population.

Defective gas appliances were found in 17 per cent of the homes. In 22

per cent of the homes other hazardous conditions were found.

Forty-seven per cent of the families interviewed were receiving other direct services from the Department of Health. This is a much higher incidence than the city-wide average, which is approximately 25 per cent of the general population.

While no ethnic, social, or religious group is exempt from accidental poisonings, the above findings indicate a higher frequency in the lower socioeconomic population groups. This is not related, however, to constitutional or inherent factors but mainly to environmental conditions. Substandard housing, overcrowding, and ignorance are predisposing contributory factors.

TABLE VIII. POISONINGS BY SIGNS AND SYMPTOMS NOTED, 1955

SIGN OR SYMPTOM	NO.
None indicated	268
Vomiting	69
Burning in mouth or throat	63
Nausea and vomiting	33
Stupor	30
Vomiting and burning in mouth or throat	15
Nausea	11
Abdominal pains	10
Nausea, vomiting, and burning in mouth or throat	9
Nausea, vomiting, stupor	8
Vomiting and stupor	6
Abdominal pains and burning in mouth or throat	5
Abdominal pains, nausea, vomiting, dyspnea, and burning in mouth or throat	5
Abdominal pains and vomiting	5
All other signs and symptoms	109
Total	646

Signs and Symptoms.—The most common symptoms noted (Table VIII) were nausea, vomiting, burning in mouth and throat, abdominal pains, and stupor. In 41 per cent no signs and symptoms were reported.

Type of Treatment.—Fifty-one per cent were treated in the emergency room and the outpatient department and only 39 per cent were hospitalized (Table IX). It is believed that some additional patients should have received the benefit of hospitalization, particularly in cases of aspirin poisoning or other salicylate intoxication and the mineral seal oil poisonings, where delayed reactions may occur though the patient may appear totally asymptomatic on admission.

TABLE IX. POISONINGS BY TYPE OF CARE, 1955

TYPE OF CARE	NO.	PER CENT
No physician's treatment	26	4
Private physicians outside of hospital	40	6
Hospital outpatient	329	51
Hospital inpatient	249	39
Other care	2	*
Total	646	100

*Less than 0.5 per cent.

In 65 per cent of the incidents stomach lavage was therapeutically employed either alone or in combination with other measures (Table X).

TABLE X. POISONINGS BY TREATMENT GIVEN, 1955

TREATMENT	NO.	PER CENT
None	38	6
Induced vomiting	60	9
Spontaneous vomiting	21	3
Stomach lavage	229	36
Medication	62	10
Lavage and medication	85	13
Lavage and vomiting	105	16
Fluids	39	6
Not stated	7	1
Total	646	100

ATTEMPTED SUICIDES

Twenty-one attempted suicides were reported (Table XI) in children ranging from 11 to 16 years of age. Age 13 was the most dangerous, accounting for nine incidents. A marked *sex* and *color* inequality was noted. Eighteen were females; three, males. Fifteen were white; five, Puerto Rican; and only one, Negro.

Agents Involved.—Aspirin was responsible for ten poisonings; barbiturates, iodine, Clorox, Dilantin, Mercurochrome, and calamine lotion were the agents involved in the others. No fatalities were reported in this group.

FATALITIES

Seven fatalities were reported in children under 16 years of age. The age range of these children was from 10 to 24 months. Four were males and three, females. Three were white, three Negro, and one, Puerto Rican.

TABLE XI. POISONINGS BY ATTEMPTED SUICIDES, CHILDREN UNDER 17 YEARS OF AGE, MARCH, 1955–FEBRUARY, 1956

AGENT	SEX AND ETHNIC GROUP	TOTAL	AGE					
			11	12	13	14	15	16
Aspirin	White female	10	1	1	3	2	3	—
Iodine	White female	1	—	—	—	—	—	—
	Puerto Rican female	1	—	—	1	—	—	1
Clorox	Puerto Rican female	2	—	—	—	—	2	—
Dilantin	White male	1	—	—	1	—	—	—
	Puerto Rican female	1	—	—	—	—	1	—
Barbiturates	White male	2	—	—	2	—	—	—
	White female	1	—	—	1	—	—	—
Mercurochrome	Puerto Rican female	1	—	—	—	1	—	—
Calamine lotion	Nonwhite female	1	—	—	1	—	—	—
Total	White male	3	—	—	3	—	—	—
	White female	12	1	1	4	2	3	1
	Puerto Rican female	5	—	—	1	1	3	—
	Nonwhite female	1	—	—	1	—	—	—
Grand total		21	1	1	9	3	6	1

The agents involved were oil of wintergreen (2), aspirin (2), camphorated oil (1), Pyribenzamine (1), and DDT, Flit with a kerosene base (1).

The mere fact that a product is mentioned by name does not imply that it is harmful but that it was ineriminated because of misuse.

Brief Histories of Fatal Cases.—

CASE 1.—A 14-month-old white male. The toxic substance was oil of wintergreen. While the mother was busy in the kitchen, the child obtained a bottle from the closet and ingested some of its contents. A 14-year-old uncle saw the child drinking it but had no idea how much was consumed. The child was immediately taken to the family physician, who ordered medication, and the child was returned to his home. However, the child continued crying. The physician was called again and ordered hospitalization. This child died two hours after ingestion of the methyl salicylate.

CASE 2.—An 18-month-old Negro female. A bottle of camphorated oil was on the dresser in the bedroom. While the mother was in the bathroom the children (four) were playing in the bedroom. The mother smelled the odor of camphorated oil and went to the bedroom to determine what the children were doing. She found the baby covered with camphorated oil and the other children also had some on their faces and bodies. The infant soon had a convulsion and was taken to the hospital, where she was admitted several hours after ingestion of the drug. At the hospital the patient had generalized convulsions, right facial twitchings and twitchings of the right leg, soon became comatose, and died four hours after admission.

CASE 3.—A 2-year-old female, Puerto Rican infant. The toxic agent was aspirin. The mother took two 5-grain tablets of aspirin. She put the bottle on the breadbox over the table. The child climbed up on a chair, obtained

the bottle, and ingested twenty-two tablets.

The mother took the child to a physician who felt that if she had ingested the quantity of aspirin the mother stated, she should be taken to a hospital, though at that time the child was totally asymptomatic and appeared well. Gastric lavage was done in the admitting room and the child was hospitalized two hours after ingestion. Several hours later the child became drowsy, had acetone breath, and urine showed 4+ acetone; hyperventilation was marked. In spite of heroic therapeutic measures, including cortisone, the child lapsed into coma and died thirteen hours after admission.

CASE 4.—Another case of aspirin poisoning occurred in a 22-month-old white male infant.

This child obtained a bottle containing 5-grain aspirin tablets from the medicine cabinet while the parents were asleep. He reached the cabinet by a step stool which his father had just made for him. When his parents awoke several hours later, the mother found the medicine chest open and a bottle of Kaopectate spilled on the sink. She thought the child had swallowed about a tablespoonful of Kaopectate. The mother inquired of the family physician, over the phone, whether this could be harmful and was assured that this amount would not be toxic. Since the child appeared perfectly well, the family visited relatives, where they remained for lunch. After lunch, the child vomited copiously and the parents diagnosed it as a "virus." Several hours after ingestion he vomited again and appeared unsteady when trying to walk.

A physician saw the child at his office and the only positive findings were labored respiration with air hunger. The child was hospitalized and the parents were questioned as to the possibility of other medicines or substances taken. The mother then remembered that the aspirin bottle was missing from their cabinet. They were 5-grain, orange-flavored tablets.

On the strength of this history a tentative diagnosis of salicylate intoxication was made.

The child was appropriately treated and within one-half hour his color was rosy and he seemed much better. Several hours later, however, the child's breathing became jerky, and respiration increased to 45 per minute. In spite of heroic therapy the child died.

After the child's death, an aspirin bottle was found under the baby's crib with only fifteen of the original sixty tablets remaining. It is worth noting that though the medicine cabinet contained fifteen other items, such as boric acid powder, tincture Merthiolate, Vicks nose drops, camphor ice, terpin hydrate, a petrolatum hair tonic, etc., and although six additional household preparations were under the sink, such as rubbing alcohol, shampoo, Clorox, Lysol, Carbona, and Florient (an air deodorant), yet no one suspected that the child ingested anything but Kaopectate.

CASE 5.—A 10-month-old white male. The toxic agent was Pyribenzamine.

The mother had antihistamine tablets in her pocketbook and gave the pocketbook to the child to play with. The child opened it, found the box containing tablets, and ingested them. As soon as the mother discovered it, the child was taken to a physician who admitted him to a hospital. On admission the child presented the following symptoms: vomiting, clonic convulsions, cyanosis, and dilated pupils. In spite of appropriate therapy this child died about eight hours after ingestion of the drug.

CASE 6.—A 14-month-old female, Negro. The toxic agent in this case was DDT, Flit with a kerosene base.

A can of DDT preparation was on the television set. An older sibling obtained it and gave it to the patient who drank its contents. The child was taken to the hospital with the following symptoms: burning in throat, and dyspnea. The child died seven hours after admission.

CASE 7.—Another fatality was reported in an 18-month-old male Negro infant who ingested oil of wintergreen which he found on a dresser. This child died eight hours after hospitalization.

In addition, eighteen fatalities in children were reported in 1955 as due to lead poisoning, out of a total of 110 occurrences. No deaths were reported from lead poisoning in children over 5 years of age. These are not included in the present report, which concerns itself only with cases on which home visits were made by public health nurses. Lead poisonings were investigated by epidemiologists from the Bureau of Preventable Diseases, as a special study, and will be reported upon at a later date.

VALUE OF HOME VISITS BY PUBLIC HEALTH NURSES

A careful analysis of the record indicates that family reaction to visits was good in 98 per cent of the cases and that a public health nurse was definitely able to help the family with other problems in 97 per cent of the cases. Because of the nurse's intimate knowledge of the geographic area involved, its inhabitants, their cultural and social characteristics, and home conditions, her previous experiences with the families, and because of her training and experience in establishing easy liaison with families, she was considered the most logical person to make the epidemiological investigations. It was also believed, and the belief was amply substantiated, that the nurse would gain easy access into homes. Families have long been sensitized to accept home visits from nurses into their homes more readily than from any other health and welfare worker.

LOCATIONS, CONTAINERS, AND RANGE OF TOXIC SUBSTANCES

One hundred thirty-seven (137) distinct chemical products were involved in these poisonings. Some drugs and preparations included several brands, ranging from one to twelve in number. This indicates the multiple availability in the average home of products which if inappropriately used may constitute a grave hazard.

The greatest majority of the injurious agents involved were in open places, such as table, floor, sink, shelf, dresser, open cabinet, etc., easily accessible, and many were not in their original containers but in "secondary" containers such as household utensils, milk bottles, saucers, cola bottles, mayonnaise jars, and drinking glasses. Climbing to obtain the substances was the most frequent device used.

Labeling.—It is not believed that proper labeling of a product in itself will be a complete solution to the problem of accidental poisoning, since in most cases the warning is stated in fine print and thus many do not read or notice the warning on the label, and many young children cannot read. It is recommended, however, that in addition to other labeling requirements, all household preparations should include on the label, in bold type, and prominently displayed, a safety warning such as "Keep this and all other household preparations out of reach of children."

Disinfectants, such as pine products and others, carry on the label the phenol coefficient value. The phenol coefficient is merely a figure denoting the disinfectant quality of a given substance but does not mean that it contains phenol. Very often physi-

cians mistakenly believe that the substance ingested contains phenol and unnecessarily subject the victims to bronchoscopic examinations, lavagic treatment, and other measures for the treatment of phenol poisonings.

inated with great frequency. It is believed that the manufacturers' unwarranted claims that the products are very nontoxic and harmless may lead to overdosages and hence to intoxications.

TABLE XII. POISONINGS BY MAJOR SUBSTANCES INGESTED BY AGE OF CHILD, 1955

SUBSTANCE	TOTAL	AGE IN YEARS					
		UNDER 1	1	2	3	4	5-15
I. *External medications and cosmetics*							
Potassium permanganate	16	1	1	6	7	1	-
Mercurochrome	8	-	5	1	1	-	1
Camphorated Oil	5	1	2	-	1	-	1
Oil of Wintergreen	5	-	1	3	-	1	-
Other external drugs	43	4	15	15	4	2	3
Cosmetics	18	2	8	8	-	-	-
II. *Internal medications*							
Baby aspirin	80	2	5	35	26	9	3
Regular aspirin	17	-	4	7	2	3	1
Barbiturates	17	-	4	7	-	3	3
Laxatives	10	-	1	5	3	1	-
Cough medicine	7	-	1	4	1	-	1
Epileptic medicine	6	-	-	1	1	1	3
Other internal drugs	54	5	2	30	7	4	6
III. *Cleaning, sanitizing, and polishing agents*							
Bleach	49	-	20	10	9	4	6
Pine oil disinfectants	27	-	13	6	3	2	3
Lye and Drano	17	-	5	6	3	3	-
CN and Lysol	17	-	9	6	2	-	-
Other cleaning, sanitizing, and polishing agents	37	2	23	8	1	-	3
IV. *Solvents and petroleum distillates*							
Benzene	16	-	11	2	3	-	-
Furniture polish and floor wax	14	1	11	2	-	-	-
Kerosene	11	-	8	2	-	1	-
Lemon oil	5	-	5	-	-	-	-
Other solvents and petroleum distillates	12	-	5	2	2	-	3
V. *Rodenticides*	18	3	6	6	2	1	-
VI. *Insecticides*							
Moth balls	14	-	7	6	1	-	-
Roach paste and other insecticides	41	3	23	11	-	1	3
VII. *Turpentine*	18	2	8	7	-	-	1
VIII. *Miscellaneous*							
Ink and ink powder	8	-	3	2	1		2
Other miscellaneous	56	5	21	13	6	3	8
Total	646	31	227	211	86	40	51

This in spite of the fact that the product does not contain phenol at all!

Nonbarbiturate Sedatives.—Many such new products are being incrim-

Poisonings Within Hospitals.—Two cases of accidental poisonings through the ingestion of chemicals on bedside night tables were reported within ten days; one due to trisodium phosphate,

and one of Zephiran chloride mixed with sodium nitrite.

A child suffering from lead intoxication, and with a known history of pica, while in the hospital for treatment was reported to have ingested crayons. Another child ingested Thorazine while a patient in the hospital.

Poisonings in Doctors' and Dentists' Children.—Physicians' and dentists' children are not infrequently reported as victims from overdosages of many products which are accessible to them from "samples." Children of detail men who distribute samples are also on our active roster.

Masked Hazards.—Particular attention must be paid to preparations which contain certain ingredients that are not mentioned on the label. For example, furniture polish often contains a high percentage of naphtha or mineral oil which does not have to be mentioned on the label, and yet naphtha is a highly toxic substance when ingested.

Vitamin preparations which contain iron are other examples, the accent being on the vitamin and not on the iron, which is often the harmful agent.

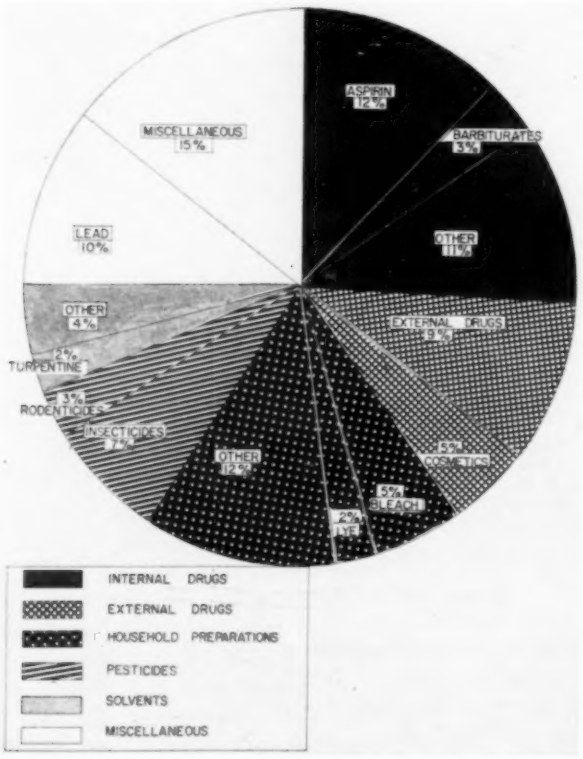

Fig. 2.—Type of poisoning in 1,151 patients under 15 years of age, 1955.

UNNECESSARY THERAPY

Gastric lavage and other therapeutic measures should not be instituted

when inert, highly diluted, and harmless preparations are involved.

SOLVING THE ACCIDENTAL POISONING PROBLEM

At the request of organized medicine in New York City, including the academies of medicine, and of pediatries, and local county medical societies, a Poison Control Center was established, to operate as a regularized activity of the New York City Health Department rather than as a hospital function.

It includes the services of several bureaus, such as the Bureau of Public Health Nursing, Preventable Diseases, Environmental Sanitation, Laboratories, Public Health Education, etc., and has the full cooperation of the Chief Medical Examiner's Office and the Department of Hospitals.

All hospitals with emergency services in New York City voluntarily agreed to participate in the program and 130 hospitals have thus designated poison control officers within their respective hospitals.

Tabulations and a complete register are kept on each hospital and for each product, as well as for each patient.

It may be pointed out, parenthetically, that the desired information is provided by the Center to the inquirers within *minutes or hours.* At times it becomes necessary for the Center to track down in a detective-like fashion the possible toxic ingredients in a new product, and no effort or expense is spared to obtain such information for the guidance of the physicians. Numerous calls have been made to manufacturers of certain products in all parts of the country.

It is doubtful whether any other single activity or program has ever gained wider acceptance and recognition by the medical profession.

Though reporting of accidents was mandatory in New York City for many years, it was negligible prior to the establishment of the Poison Control Center.

During the first nine months of operation, however, 3,000 poisonings were reported. Failure to report by private physicians, however, is still a gross inadequacy.

The following is a typical sample of poisonings recorded in a recent twenty-four-hour period:

Incident 1.—Turpentine; 6-year-old male child. The child was playing in the cellar and reached up for a coffe can on a shelf. The can was uncovered, it tipped, and turpentine splashed all over the child's face and eyes.

Incident 2.—Lye; 19-month-old male child. The child was playing on a chair in the kitchen, and put his finger into a can containing lye, and then put his finger in his mouth.

Incident 3.—DDT; 2-year-old male child. While mother was in the kitchen, the child went into the bedroom, where a can of DDT spray was placed on the bureau. The child ingested some of the contents.

Incident 4.—Aspirin; 2-year-old female child. Three children in the same household were playing alone. The 2-year-old child climbed up to the medicine cabinet in the bathroom, obtained a bottle of aspirin and cough syrup, and ingested twenty-five tablets of aspirin and some of the syrup.

Incident 5.—Aspirin; 3-year-old male child. The mother gave a younger sibling two tablets of baby aspirin. She left the bottle on the sink in the kitchen. The 3-year-old child obtained the bottle and ingested twenty-four tablets.

Incident 6.—Aspirin; 18-month-old female child. While parents were asleep, the child climbed up in her chair and ingested eighteen 5-grain tablets of aspirin which were in a bottle on a dresser in the bedroom.

Incident 7.—Aspirin; 16-month-old male child. The child was suffering from an infection for which aspirin was prescribed.

The mother administered 2½-grain flavored aspirin tablets every two hours for three days. The child showed signs of aspirin intoxication, and was taken to a hospital for treatment.

Incident 8.—Aspirin; 1-year-old male child. The child's 3-year-old brother brought aspirins into the bedroom and gave them to the child while the mother was asleep. The child was hospitalized for four days.

Incident 9.—Potassium permanganate; 3½-year-old child. While visiting grandparents, the child went into the bedroom to play. He found the tablets and ingested one. At first the parents thought it was ink, but soon recalled that potassium permanganate had been placed in the dresser drawer in the bedroom, for the use of the grandfather, who had a fungous infection of the feet.

Incident 10.—Benzene; 1½-year-old male child. While playing in the kitchen, the child opened the closet door and obtained a bottle of benzene and ingested some of its contents.

Incident 11.—J-O paste; 1-year-old female child. The baby was in the kitchen alone, and obtained some of the J-O paste, which he put in his mouth and over his clothes.

Incident 12.—Tru-Tox insecticide; 14-month-old female child. The child was under the supervision of a 12-year-old baby sitter. She went into the kitchen closet, obtained a bottle of insecticide from the shelf (a very low shelf), and ingested some of the contents.

Incident 13.—Vicks Vapo-Rub; 5-year-old female child. The child had a cough, and the family was in the habit of taking this medication for coughs and colds. The mother told the older brother to give the child this medication, needed to stop the cough. The child was given a tablespoonful of this medication, and soon developed nausea, vomiting, convulsions, and other symptoms, about three-quarters of an hour after ingestion. The child was hospitalized, and made a complete recovery.

Another child who ingested Vicks Vapo-Rub also had convulsions. The above episodes are but a few of the numerous reports received daily, and illustrate clearly the relationship of ready access of drugs and household preparations to the occurrence of poisonings.

Location of Poison Control Center.—It is believed that the best location of a Poison Control Center is within the confines of a Health Department. Health Departments are geared to prevention, have a know-how of epidemiology, and provide community-wide services. They also contain all the ancillary services needed, such as laboratories, nursing, sanitary engineering, statistics, health education, etc., for the successful operation of such a program.

DISCUSSION

There is no simple solution to the problem of the complexity of the potential poisoning agents. New items and the changing nature of commercial products make reference material of very limited value. In addition, not only the injurious agents but also the total environment, and the human factors as well as the psychodynamics involved, must be investigated and understood. In order to institute appropriate countermeasures, it is essential to analyze in detail modes of occurrences, when, where, how, to whom, and why accidental poisonings happen. There is also great need for investigative research in order to explore not only the causes but also the modes of prevention. The problem, however, though complex and perplexing, does not appear hopeless. A few unmistakable facts emerge from this study:

1. The under-5-year age group is the most susceptible, and accidents are intimately linked with the child's stage of growth and development.

2. Poisonings are in direct proportion to availability and accessibility of agents.

3. Though the number of products involved are legion and their number is growing daily, most of the poisonings were due to the "ordinary," everyday drugs and preparations used in the home. Thus, if due emphasis were placed on the susceptible groups and substances most often involved, about two-thirds of the accidents could be prevented.

4. Treatment is *secondary* since lavage was the mode of therapy predominantly used or indicated. The goal must be *prevention*.

The physician is already alert to many of the problems in preventive medicine. He should prove just as competent and skillful in the control of accidental chemical poisonings. Home safety and accident prevention must become a part of the practice of medicine and of pediatrics in particular. The physician is in the most strategic line of communication with families. He is frequently in the homes of families, and members of families are frequently in his office.

Education.—The primary and most important step in the poisoning control program is education. The final success of this program will depend largely on the degree of involvement and participation of the individual practicing physician.

It is important for the physician to have a wider knowledge about the epidemiology of accidents, the dynamics of the problem, and particularly about modes of prevention. As a matter of fact, the education of the physician should begin at the *undergraduate level*. Accident prevention and home safety should be included as part of pediatric training in the medical schools.

The physician also has knowledge of the child's growth and development, family background, physical, cultural, and social environment, and the child's habits and attitudes. This provides an unparalleled opportunity to advise parents on the potential hazards at a given stage of growth and development and their prevention.

The physician is in a strategic position to observe any safety hazards in the home and to provide needed health education, guidance, and safety information.

The physician should include a query about accidents whenever a history is obtained on a patient in the same manner as he inquires about past or present illnesses. The question about accidents should be an integral part of the medical record. This practice should be followed not only in his office but also in hospitals and dispensaries whenever and wherever patients are interviewed.

The physician's waiting room should also contain health education literature and other visual aids about the accidental poisoning problem and how to prevent such occurrences.

Meticulous Written Instructions.—Such directions should be given to patients whenever medications are prescribed. The dosage, brand, and time interval must be clearly stated. Only small quantities to fill current needs should be ordered. It is important that sufficient emphasis be laid on the need to keep such medications, and all drugs and household preparations, out of reach of children and under lock and key. Care must be exercised not to dispense "samples" in envelopes without specific instructions and due caution about safekeeping.

Advice also must be given on keeping drugs in original containers.

Self-medications should also be strongly discouraged.

Prompt and accurate reporting of accidents to the local health department is also of inestimable value in the poisoning control program. It is only through a study and scrutiny of the epidemiological data that sound preventive programs can be formulated.

SUMMARY AND CONCLUSIONS

1. Data are presented on 646 chemical poisonings in children under 16 years of age, to whom home visits were made by public health nurses.

2. Eighty-one per cent of all poisonings in this group occurred in ages 1, 2, and 3. The type of poisoning is intimately linked with the child's stage of growth and development.

3. Internal preparations were responsible for 29 per cent of all accidents and aspirin is the chief offender in this group.

4. A close association between accessibility and occurrence has been established. Removal of a substance from an original container is also a contributory factor.

5. A definite correlation also exists between socioeconomic level and incidence, being higher in the lower socioeconomic levels.

6. No statistically significant sex difference was observed but there is a marked color variation, incidence being higher in the nonwhite group.

7. Ignorance rather than carelessness was a contributory factor.

8. A Poison Control Center—a new approach in prevention.

9. A dynamic and comprehensive control program is indicated.

10. Immediate and appropriate application of factual data to the most susceptible population will result in significant reductions in morbidity and mortality from accidental poisonings.

11. Further research is needed; standardization of dosages, packaging, labeling, advertising methods, etc., need to be investigated further.

12. It is a medicosocial, community-wide problem and all disciplines must collaboratively play an active role in its prevention.

13. Health education is a most effective tool and the family physician can play a dominant role in the poisoning control program.

Grateful acknowledgments are expressed to Mrs. Florence Rich and Miss Frieda Greenstein of the Bureau of Records and Statistics for their invaluable aid in compiling the statistical data herein presented. Sincerest thanks are also expressed to all public health nurses who so diligently made the home visits and who contributed so much to the program.

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SPEECH

OF

CHARLES DICKENS, Esq.,

As Chairman at the Dinner

ON BEHALF OF THE

HOSPITAL FOR SICK CHILDREN,

FEB. 9, 1858.

SPEECH OF

CHARLES DICKENS, ESQ.,

ON BEHALF OF THE

Hospital for Sick Children,

49, GREAT ORMOND STREET.

PATRON,—HER MAJESTY THE QUEEN.

The Objects of the Institution are—

I.—The Medical and Surgical Treatment of Poor Children.

II.—The Attainment and Diffusion of Knowledge regarding the Diseases of Children.

III.—The Training of Nurses for Children.

London:

PRINTED BY FOLKARD AND SON, DEVONSHIRE STREET, QUEEN SQUARE.

1867.

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The Hospital is open for Public Inspection daily between the hours of 12 and 4.

SPEECH

OF

CHARLES DICKENS, Esq.,

At Freemasons' Hall, February 9th, 1858.

"Ladies and Gentlemen,

"It is one of my rules in life not to believe a man who may happen to tell me that he feels no interest in children. I hold myself bound to this principle by all kind consideration, because I know, as we all must, that any heart which could really toughen its affections and sympathies against those dear little people must be wanting in so many humanising experiences of innocence and tenderness, as to be quite an unsafe monstrosity among men; therefore I set the assertion down, whenever I happen to meet with it—which is sometimes, though not often—as an idle word, originating possibly in the genteel languor of the hour, and meaning about as much as that knowing social lassitude, which has used up the cardinal virtues and quite found out things in general, usually does mean. I suppose it may be taken for granted that we, who come together in the name of children, and for the sake of children, acknowledge that we have an interest in them; indeed, I have observed since I sat down here that we are quite in a child-like state altogether, representing an infant institution, and not even yet a grown-up company. A few years are necessary to the increase of our strength, and the expansion of our figure; and then these tables, which now have a few tucks in them, will be let out, and then this hall, which now sits so easily upon us, will be too tight and small for us. (Cheers

and laughter.) Nevertheless, it is likely that even we are not without our experience now and then of spoilt children. I do not mean of our own spoilt children, because nobody's own children ever were spoilt — (laughter) — but I mean the disagreeable children of our particular friends. (Laughter.) We know by experience what it is to have them down after dinner, and, across the rich perspective of a miscellaneous dessert, to see, as in a black dose darkly, the family doctor looming in the distance. (Much laughter.) We know—I have no doubt we all know—what it is to assist at those little maternal anecdotes and table entertainments, illustrated with imitations and descriptive dialogue, which might not be inaptly called, after the manner of my friend Mr. Albert Smith, the toilsome ascent of Miss Mary and the eruption (cutaneous) of Master Alexander. (Laughter.) We know what it is when those children won't go to bed; we know how they prop their eyelids open with their forefingers when they will sit up; how, when they become fractious, they say aloud that they don't like us, and our nose is too long, and why don't we go? And we are perfectly acquainted with those kicking bundles which are carried off at last protesting. (Cheers and laughter.) An eminent eye-witness told me that he was one of a company of learned pundits who assembled at the house of a very distinguished philosopher of the last generation, to hear him expound his stringent views concerning infant education and early mental development, and he told me that, while the philosopher did this in very beautiful and lucid language, the philosopher's little boy, for his part, edified the assembled sages by dabbling up to the elbows in an apple pie which had been provided for their entertainment, having previously anointed his hair with the syrup, combed it with his fork, and brushed it with his spoon. (Renewed laughter.) It is probable that we also have our similar experiences, sometimes, of principles that are not quite practice, and that we

know people, claiming to be very wise and profound about nations of men, who show themselves to be rather weak and shallow about units of babies.

"But, ladies and gentlemen, the spoilt children whom I have to present to you after this dinner of to-day are not of this class. I have glanced at these for the easier and lighter introduction of another, a very different, a far more numerous, and a far more serious class. The spoilt children whom I must show you are the spoilt children of the poor in this great city—the children who are, every year, for ever and ever irrevocably spoilt out of this breathing life of ours by tens of thousands, but who may, in vast numbers, be preserved, if you, assisting and not contravening the ways of Providence, will help to save them. (Cheers.) The two grim nurses, Poverty and Sickness, who bring these children before you, preside over their births, rock their wretched cradles, nail down their little coffins, pile up the earth above their graves. Of the annual deaths in this great town, their unnatural deaths form more than one-third. I shall not ask you, according to the custom as to the other class—I shall not ask you, on behalf of these children, to observe how good they are, how pretty they are, how clever they are, how promising they are, whose beauty they most resemble—I shall only ask you to observe how weak they are, how like death they are! And I shall ask you, by the remembrance of everything that lies between your own infancy and that so mis-called second childhood, when the child's graces are gone, and nothing but its helplessness remains,—I shall ask you to turn your thoughts to *these* spoilt children, in the sacred names of Pity and Compassion.

"Some years ago, being in Scotland, I went with one of the most humane members of the humane medical profession, on a morning tour among some of the worst-lodged inhabitants of the old town of Edinburgh. In the closes and wynds of that picturesque place—I am sorry to remind you what

fast friends picturesqueness and typhus often are —we saw more poverty and sickness in an hour than many people would believe in a life. Our way lay from one to another of the most wretched dwellings—reeking with horrible odours—shut out from the sky—shut out from the air—mere pits and dens. In a room in one of these foul places, where there was an empty porridge-pot on the cold hearth, with a ragged woman and some ragged children crouching on the bare ground near it—where, I remember as I speak, that the very light, reflected from a high damp-stained and time-stained house wall, came trembling in, as if the fever which had shaken everything else there had shaken even it—there lay, in an old egg-box, which the mother had begged from a shop, a little feeble, wasted, wan, sick child. With his little wasted face, and his little hot worn hands folded over his breast, and his little bright attentive eyes, I can see him now, as I have seen him for several years, looking steadily at us. There he lay in his little frail box, which was not at all a bad emblem of the little body from which he was slowly parting,—there he lay quite quiet, quite patient, saying never a word. He seldom cried, the mother said; he seldom complained; 'he lay there seeming to woonder what it was a' aboot.' God knows I thought, as I stood looking at him, he had his reasons for wondering —reasons for wondering how it could possibly come to be that he lay there, left alone, feeble and full of pain, when he ought to have been as bright and as brisk as the birds that never got near him—reasons, for wondering how he came to be left there, a little decrepid old man, pining to death, quite a thing of course, as if there were no crowds of healthy and happy children playing on the grass under the summer's sun within a stone's throw of him, as if there were no bright, moving sea on the other side of the great hill overhanging the city; as if there were no great clouds rushing over it as if there were no

life, and movement, and vigour anywhere in the world—nothing but stoppage and decay. There he lay looking at us, saying in his silence, more pathetically than I have ever heard anything said by any orator in my life, 'Will you please to tell me what this means, strange man? and if you can give me any good reason why I should be so soon so far advanced upon my way to Him who said that children were to come into His presence, and were not to be forbidden, but who scarcely meant, I think, that they should come by this hard road by which I am travelling—pray give that reason to me, for I seek it very earnestly, and wonder about it very much;' and to my mind he has been wondering about it ever since. Many a poor child, sick and neglected, I have seen since that time in this London; many a poor sick child I have seen most affectionately and kindly tended by poor people, in an unwholesome house and under untoward circumstances, wherein its recovery was quite impossible; but at all such times I have seen my poor little drooping friend in his egg-box, and he has always addressed his dumb speech to me, and I have always found him wondering what it meant, and why, in the name of a gracious God, such things should be!

"Now, ladies and gentlemen, such things need not be, and will not be, if this company, which is a drop of the life-blood of the great compassionate public heart, will only accept the means of rescue and prevention which it is mine to offer. Within a quarter of a mile of this place where I speak, stands a courtly old house, where once, no doubt, blooming children were born, and grew up to be men and women, and married, and brought their own blooming children back to patter up the old oak staircase which stood but the other day, and to wonder at the old oak carvings on the chimney-pieces. In the airy wards, into which the old state drawing-rooms and family bedchambers of that house are now converted, are such little patients that the attendant nurses look

like reclaimed giantesses, and the kind medical practitioner like an amiable Christian ogre. Grouped about the little low tables in the centre of the rooms are such tiny convalescents that they seem to be playing at having been ill. On the dolls' beds are such diminutive creatures, that each poor sufferer is supplied with its tray of toys; and, looking around, you may see how the little tired, flushed cheek has toppled over half the brute creation on its way into the ark; or how one little dimpled arm has mowed down (as I saw myself) the whole tin soldiery of Europe. On the walls of these rooms are graceful, pleasant, bright childish pictures. At the beds' heads, are pictures of the figure which is the universal embodiment of all mercy and compassion,—the figure of Him who was once a child Himself, and a poor one. Besides these little creatures on the beds, you may learn in that place that the number of small Out-patients brought to that house for relief, is no fewer than ten thousand in the compass of one single year. In the room in which these are received, you may see against the wall a box, on which it is written, that it has been calculated, that if every grateful mother who brings a child there will drop a penny into it, the Hospital funds may possibly be increased in a year by so large a sum as forty pounds. And you may read in the Hospital report, with a glow of pleasure, that these poor women are so rerespondent as to have made, even in a toiling year of difficulty and high prices, this estimated forty, fifty pounds. (Cheers.) In the printed papers of this same Hospital, you may read with what a generous earnestness the highest and wisest members of the medical profession testify to the great need of it; to the immense difficulty of treating children in the same hospitals with grown-up people, by reason of their different ailments and requirements; to the vast amount of pain that will be assuaged, and of life that will be saved through this Hospital—not only among the poor, observe, but among the prosperous

too, by reason of the increased knowledge of children's illnesses, which cannot fail to arise from a more systematic mode of studying them. Lastly, gentlemen, and, I am sorry to say, worst of all—(for I must present no rose-colored picture of this place to you—I must not deceive you), lastly—the visitor to this Children's Hospital, reckoning up the number of its beds, will find himself perforce obliged to stop at very little over thirty*; and will learn, with sorrow and surprise, that even that small number, so forlornly, so miserably diminutive, compared with this vast London, cannot possibly be maintained, unless the Hospital be made better known; I limit myself to saying better known, because I will not believe that in a Christian community of fathers and mothers, and brothers and sisters, it can fail being better known, to be well and richly endowed. (Cheers.) Now, ladies and gentlemen, this, without a word of adornment—which I resolved when I got up not to allow myself—this is the simple case. This is the pathetic case, which I have to put to you; not only on behalf of the thousands of children who annually die in this great city, but also on behalf of the thousands of children who live half-developed, racked with preventible pain, shorn of their natural capacity for health and enjoyment. If these innocent creatures cannot move you for themselves, how can I possibly hope to move you in their name?

The most delightful paper, the most charming essay, which the tender imagination of Charles Lamb conceived, represents him as sitting by his fireside on a winter night, telling stories to his own dear children, and delighting in their society, until he suddenly comes to his own solitary batchelor self, and finds that they were but dream-children, who might have been but never were. 'We are nothing,' they say

* The liberal response made to this appeal enabled the Committee to increase the number of beds for In-patients from thirty-two to forty-four. In the summer of 1865 additional wards were opened, and the number of In-patients increased to 75. See a Table of admissions at page 11.

to him; 'less than nothing and dreams. We are only what might have been, and we must wait upon the tedious shore of Lethe, millions of ages, before we have existence and a name.' 'And immediately awaking,' he says, 'I found myself in my arm-chair.' The dream-children whom I would now raise, if I could, before every one of you, according to your various circumstances, should be the dear child you love, the dearer child you have lost, the child you might have had, the child you certainly have been. Each of these dream-children should hold in its powerful hand one of the little children now lying in the Child's Hospital, or now shut out of it to perish. Each of these dream-children should say to you, 'O, help this little suppliant in my name; O, help it for my sake!' Well!—and immediately awaking, you should find yourselves in the Free-masons' Hall, happily arrived at the end of a rather long speech, drinking 'Prosperity to the Hospital for Sick Children,' and thoroughly resolved that it shall flourish." (Loud cheers.)

The following Summary will show the progress which has been made during the fifteen years since the opening of the Hospital in 1852.

	In-Patients.	Out-Patients.
1852	143	1250
1853	190	4251
1854	251	6721
1855	265	8087
1856	309	9995
1857	325	9025
1858	380	9773
1859	411	9867
1860	384	8833
1861	577	10,772
1862	543	9,615
1863	571	11,670
1864	581	11,523
1865	658	11,800
1866	771	11,939
	6359	135,121

The Annual Report for the past year may be had on application to the Secretary at the Hospital.

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Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

FIRST ADMISSION.—The patient was a 5½-year-old girl who had been well until three weeks prior to admission, when she began to complain of periumbilical abdominal pain unrelated to meals. These recurred intermittently and increased in severity until admission. She had backache, neck pains, apathy, weakness, anorexia, polyuria, and polydipsia, but no headache, bowel disturbances, vomiting, or visual disturbances. She was admitted to another hospital one week prior to entry here, where fever of 104° F., blood pressure of 150/100, and abdominal tenderness were noted. She was started on penicillin and sulfadiazine. Because of decreasing intake, however, sulfadiazine was discontinued after a few days. When she failed to improve, she was transferred to The Children's Medical Center.

She had had frequent sore throats until the year before entry, when tonsillectomy and adenoidectomy were performed. At 3 years of age she had a generalized clonic convulsion lasting one or two minutes and was seen at The Children's Medical Center for suspected poliomyelitis. She had pharyngitis and a temperature of 102° F., but lumbar puncture was normal and the urine showed occasional hyaline casts, rare red and white blood cells, and no albumin. There were no other significant incidents in the past history and no familial diseases.

On physical examination the temperature was 102.2° F., the pulse 148, and the respirations 24. The blood pressure was 190/138 right arm, 186/130 left arm, 180/130 right leg, 190/130 left leg. The height was 42 inches, the weight 33 pounds. The child was pale, irritable, and appeared acutely and chronically ill. There were many petechiae in the antecubital fossae. The fundi showed narrowing of the arterioles, arteriovenous nicking, hemorrhages and exudates, and papilledema bilaterally. There was a small amount of crusted blood about the anterior nares, and the lips were cracked and bleeding. The heart was slightly enlarged, the aortic second sound was greater than the pulmonic second sound, and a grade II systolic blowing murmur was heard maximal at the upper left sternal border. The abdomen was flat, with tenderness throughout and considerable voluntary spasm, but no rebound tenderness; no organs or masses were palpable. Rectal examination revealed a mass high in the right pelvis. The remainder of the physical examination was negative.

Repeated urinalyses disclosed the following findings: pH 5.5 to 7.0, specific gravity 1.003 to 1.006, albumin 0 to 3+, red cells varied from only 1 or 2 per high-power field to grossly bloody, and the white cells from 2 or 3 per high-power field to "loaded." Several days after admission bacteria were seen and culture on two occasions grew *Aerobacter aerogenes* and one was sterile. The blood hemoglobin was 7.5 grams per cent. The red cell count was 2.45 million, the white cell count 11,000 to 23,000; the differential showed 64 polymorphonuclear leukocytes, 11 lymphocytes, 1 eosinophil, 20 band forms, 4 monocytes; total eosinophils, 126. The platelets numbered 25,000 to 125,000. Repeated nonprotein nitrogen ranged from 17.6 to 25 mg. per cent; the plasma pH was 7.5 on three occasions. The CO_2 was 28.5 to 34.4, the sodium 130 to 142, the chloride 83 to 99, and the potassium 5.1 to 3.5 meq. per liter. The calcium was 7.1 to 8.0 mg. per 100 ml., and the phosphorus 3.4 to 3.6 mg.; the sedimentation rate was 25 mm. per hour. The Hinton and tuberculin tests were negative. The bleeding and clotting times were normal. The Rumpel-Leede test was positive. The prothrombin time was 20 seconds; control, 17 seconds. The phenolsulfonphthalein value ranged from 36.5 per cent in two hours. The urea clearance was 79 per cent of normal. An x-ray film of the chest showed the heart to be at the upper limits of normal in size, films of the knee showed slight undermineralization, and a plain film of the abdomen showed no abnormalities. An electrocardiogram showed left ventricular hypertrophy with strain.

Studies were first done to evaluate the child's concentrating ability but she lost 1 pound after a twelve-hour dry period, urine concentration reached only to 1.006, and she seemed very dry clinically. A surgical consultant felt a mass by rectum and on heavy sedation this could be felt on the abdominal examination, deep in the right pelvis. An intravenous pyelogram showed prompt excretion of dye on the left, with good concentration and minimal rounding of the calyces. At fifteen minutes there was abnormal collection of dye over the first sacral segment on the right. The bladder was large.

The patient was given a low-salt diet and intravenous Veriloid, with transient reduction of the blood pressure to 150/100 levels, cessation of polydipsia, and increase of specific gravity of the urine to 1.012. However, the hypertension recurred, to 200/150, and there were tarry stools. Cystoscopy revealed sterile urine in the left ureter, with rare red and white blood cells and a trace of albumin. The right ureter was seen but could not be entered. Dye appeared promptly at both ureteral orifices. She was discharged after one month on bed rest, Aureomycin, oral penicillin, and Feosol.

Second Admission.—Although the child did well at first, vomiting and abdominal pain recurred and she was readmitted to the hospital, three and one-half months later.

The blood pressure was 248/208, the temperature 98.6° F., the pulse 120, and the respirations 26. Physical examination was the same as on the previous admission. Repeat laboratory studies showed no changes except for a persistently higher hemoglobin (13 to 14 grams per cent). Intravenous and oral Veratrum alkaloids had no affect on the blood pressure.

On the fifteenth hospital day operation was performed.

DISCUSSION

DR. GUSTAVE DAMMIN.*—In the first paragraph of the protocol, the points of major interest to me appear to be the record of intermittent abdominal pain, backache, polyuria, polydipsia, and hypertension. There was no record of headache, visual disturbances, bowel disturbances, or vomiting. The visual disturbances must have occurred later, at the time when the fundi were noted to show significant changes. We note that when the patient was first seen she had a fever of 104° F., abdominal tenderness, and was treated with penicillin and sulfadiazine. On admission to the hospital, again, she had fever, rapid pulse rate, moderately rapid respirations, and a blood pressure that is recorded as equal in all four extremities, with both high systolic and diastolic values. A height of 42 inches and a weight of 32 pounds would indicate some weight lack of perhaps 8 or 10 pounds. The description of the patient is important. She was irritable, acutely and chronically ill, and pallid. The pallor could be ascribed to the anemia. The petechiae and the changes in the fundi were consistent with hypertension. The heart was slightly enlarged. The findings in the abdomen consisted of tenderness with voluntary spasm and, on rectal examination, a mass high in the right pelvis.

The initial urinalysis disclosed a pH reaction of 5.5 and a specific gravity of 1.003, which is good evidence that this was not chronic bilateral renal disease with demonstrated ability to dilute to that level. It must mean that if there was any renal impairment at all, it would be explained by a unilateral lesion. The albumin, the urinary red and white cell counts, and the absence of casts may indicate some focal urinary tract damage that could be related to the hypertension. The hemoglobin was 7.5 grams per cent, the erythrocyte count 2.45 million, and the leukocyte count 11,000 per cubic millimeter, with a normal differential. In considering the evidence of anemia in conjunction with a nonprotein nitrogen of 17.6, a blood pH of 7.5, and a CO_2 of 28.5 mg. per cent, we have further indication that we are not dealing with a chronic bilateral renal lesion with insufficiency that gave rise to hypertension. Thus, the anemia was not the result of the renal disease, because of the absence of nitrogen retention and acidosis. Was this blood loss or hemolysis? No mention has been made of jaundice. I believe that with this clinical picture we are dealing with blood loss that might be related to a diffuse vascular lesion, possibly involving the vessels of the gastrointestinal mucosa.

The lesions that I have under consideration are the following: (1) A unilateral renal lesion, associated with obstruction, producing a large kidney which was perhaps lower than its normal position, with hydronephrosis, so that it might be palpable as a mass in the right flank. (2) An intrarenal tumor producing hypertension. There are perhaps a half dozen cases recorded, in which a Wilms' tumor was associated with hypertension, not to this degree, but significant hypertension, which was relieved by removal of the tumor. (3) An extrarenal tumor with

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secondary effects on the ureter in the form of obstruction. (4) An extrarenal tumor of a type that by itself would be associated with hypertension, namely, a pheochromocytoma. (5) Polyarteritis involving the renal artery and producing hypertension by a reduction of renal arterial flow. Against that would be absence of nitrogen retention. However, that is not necessarily present, and an aneurysm might form on a renal artery, and might produce enough retroperitoneal and perinephric hemorrhage, so that the kidney would be palpated as enlarged and a mass felt in the right pelvis.

I would like to know about the plain film of the abdomen and the intravenous pyelogram, and information obtained by cystoscopy and perhaps retrograde pyelography.

DR. E. B. D. NEUHAUSER.—The chest film shows a hypertensive contour of the heart and great vessels. The heart is definitely enlarged, with a presumed left ventricular hypertrophy, and the aorta for a child of 4 is unduly prominent. It appears elongated, and there is a prominent aortic knob. There is one film of an intravenous urogram and I believe in the left upper corner of the film you can see there is early good excretion of Diodrast in the left kidney; the kidney was quite normal in size and contour. Overlying the first sacral segment, slightly to the right of the midline, there is an irregular collection of opaque material. The soft-tissue shadow itself, which is associated with this, could not be well outlined but appeared to be a kidney. A retrograde examination was attempted and I believe that only the left ureteral orifice could be entered. The x-ray diagnosis was atrophic pelvic kidney, without evidence of hydronephrosis.

There is one further examination done just a few days ago. A repeat intravenous urogram shows normal function, but, in view of Dr. Dammin's discussion so far, it is of interest that the patient now has a considerable number of opaque gallstones.

DR. LOUIS K. DIAMOND.—Do these appear on the original films?

DR. NEUHAUSER.—No, I do not believe that they would project.

DR. DAMMIN.—Were there any tests done using histamine, Mecholyl, benzodioxane, or Regitine, to determine the blood pressure response of this patient?

DR. ROBERT HAGGERTY.—No, these were not done since the lesion was thought to be intrinsic to the ectopic kidney.

DR. DAMMIN.—Can we tell from the physical examination whether the size of the mass would correspond to a normal-sized kidney in an unusual location or an atrophic kidney?

DR. HAGGERTY.—Yes, it was believed to be a normal-sized kidney.

DR. DAMMIN.—In that case, one would be faced with trying to explain all the clinical manifestations on the presence of an ectopic kidney which at times, perhaps, took part in the general manifestations of a diffuse arteriolar disease and may have accounted for the presence of occasional blood and possibly the white cells in the urinary sediment. With the mass recognized as an ectopic, normal-sized kidney, we are still faced with trying to explain some of the clinical manifestations,

such as polydipsia, polyuria, and the very high blood pressure. The fever could be explained by pyelonephritis in an ectopic kidney having an abnormal ureteral communication. The kidney on the other side was functioning normally, judging from the pyelography and the laboratory tests. With the demonstrated size of the pelvic kidney, we do not have to consider an intrarenal tumor as a cause of hypertension. But an abnormally located kidney, with a disturbed ureteral communication, and one subject to pyelonephritis, may have been undergoing atrophy. The clinical manifestations do not seem to fit with an acute pyelonephritis, which would have been one of the diagnoses made on initial examination, after which the patient was treated for an infection. I would still entertain the possibility that the hypertension, even though we have an ectopic kidney, was related to another lesion, since acute pyelonephritis by itself is not a cause for hypertension. Because of a few elements in the history, such as the polydipsia, the polyuria, the level of the hypertension, and the diffuse arteriolar disease, I would like to have seen tests done with histamine, Mecholyl, benzodioxane, and Regitine, which should tell whether or not a pheochromocytoma was the cause of the elevated blood pressure.

Dr. Charles D. Cook.—I think this child certainly taught us a lesson, and that is when dealing with a severe progressive and really desperate illness, fairly heroic therapeutic measures are certainly indicated. This child was seen by many people on the staff, was seen in consultation by the surgical service and by people from outside the hospital, and everybody felt that this child very likely had the diagnosis Dr. Dammin suggested. Most observers believed that some abnormality of her renal pelvis was the prime cause of the hypertension. It was also widely believed by many, including the surgical staff, that the hypertensive disease, whatever its cause, was too far advanced to make surgery safe, or to be reversible. Consequently, definitive surgical therapy was not carried out and the patient was discharged home to her private physician. Dr. Sands should take the entire credit for this child's subsequent course. He pushed everybody in the hospital into taking more definitive steps to effect a cure.

Dr. Kenneth F. Sands.—According to the history, at the age of 4 years this child had generalized clonic convulsions but no blood pressure was recorded; I think she might well have had hypertension at that time.

Dr. Diamond.—I remember at the time we thought her bleeding tendency was part of a generalized vascular disease, whether caused by the hypertension directly or by a disease underlying the hypertension. She had platelet levels that were low or low normal. She had a reticulocyte level that seemed to be a response to her bleeding. We found no evidence of hemolytic disease. Subsequently, after transfusion, she retained her blood level quite well and there was no further suggestion of hemolytic disease.

Dr. Douglas T. Davidson, Jr.—I would like to point out that brain-wave activity as an indication of the health of the nervous tissue of the brain is a very sensitive indicator of general systemic metabolism; it responds to all

sorts of electrolyte imbalances. In this connection, I recall having followed a series of electroencephalograms on a patient who had hypertensive encephalopathy due to an aberrant renal artery, and it proved interesting to see the gross nature of the electroencephalographic changes at a time when she had little to show in the way of mental aberration, and the rate of reversal of these changes was considerably slower and much less perfect than the return of the blood pressure.

DR. EDNA SOBEL.—A pheochromocytoma could lie above the kidney and displace it downward, but I would have thought that the gastrointestinal series would have given some idea of the presence of such a retroperitoneal mass.

The benzodioxane would elevate the hypertension further, for cases of essential hypertension respond with a further elevation in pressure, the positive test for pheochromocytoma being any depressed response.

DR. DAMMIN.—When one takes into account the cardiac enlargement at this stage, with a relatively short clinical course, one has to assume that there was something going on for much longer than the history indicates, and if there was an ectopic kidney, it was undergoing atrophy from the time of some infection, which is somewhat suggestive here from urine cultures and sediment studies.

DR. JOHN M. CRAIG.—The removed kidney was normal in weight but had an irregular, globular shape. There were no scars on the surface. The main renal artery was normal and divided fairly promptly into two major branches. One of these was found to be blocked for a distance of about 3 mm. along the artery by a mass which, grossly, completely filled it. It was formed microscopically by a mass of fibrous tissue, preserved and also degenerated internal elastic tissue, and a few mononuclear cells (Fig. 1). In the sections of the kidney parenchyma there was a good deal of arterial and arteriolar damage (Figs. 2 and 3). Associated with, and we believe secondary to, this damage, there was scarring of the glomeruli and atrophy of the associated tubules (Fig. 4). Some of the atrophic epithelium contained considerable hemosiderin. These areas were, however, not so marked in extent to indicate that any gross atrophy of the kidney had occurred. The minor inflammatory reaction that was present was consistent with the degree of atrophy. The pelvis was not dilated and no obstructive hydronephrosis was found.

These are very interesting findings to me, because Leadbetter and Burklund[1, 2] at Tufts Medical School have described a similar case in a child who had a pelvic kidney on the right side, with an identical lesion in the renal artery. That child also had hypertension, which was also relieved by operation. The child at 10 years of age had a perfectly normal blood pressure and renal function. The only difference between that child and this is that that child showed none of the arteriolar and arterial changes and degenerative changes secondary to the arteriolar changes in the kidney. Those authors thought that this represented a malformation of the smooth muscle and fibrous tissue of the artery wall. The same findings were present in our material. I believe that this represents an unusual case, with only

Fig. 1.

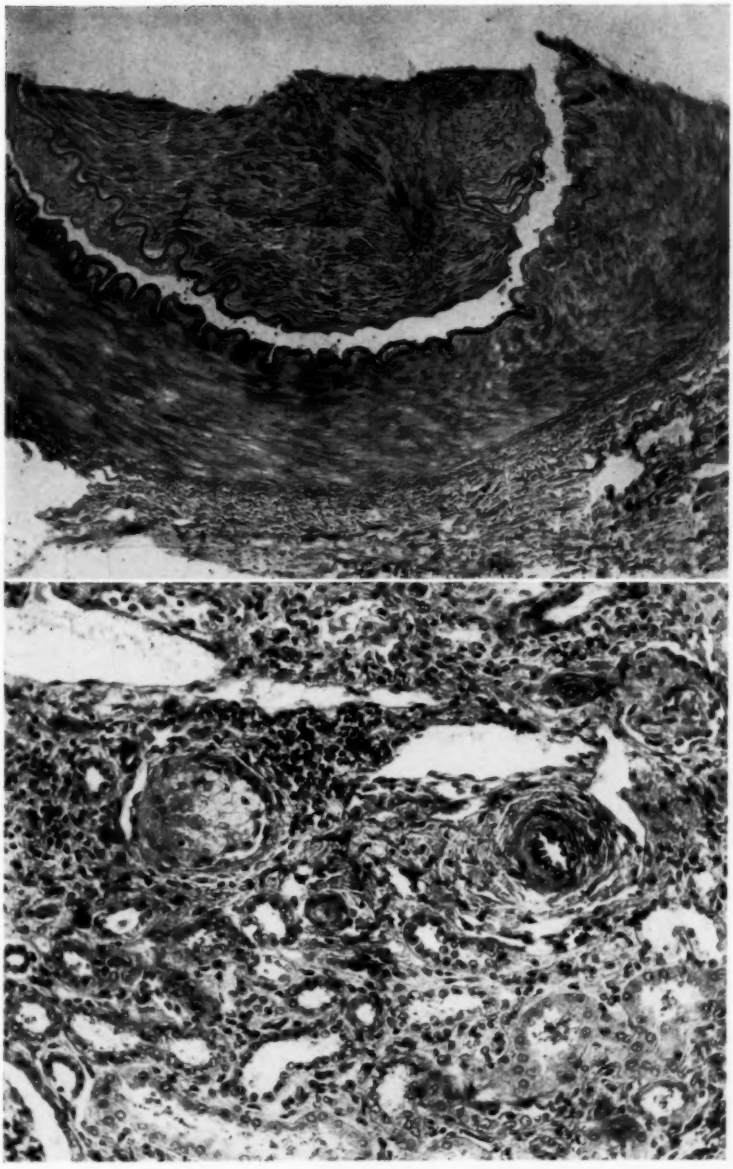

Fig. 2.

Fig. 1.—Photomicrograph of renal artery. The section is through the occluding fibrous and muscle tissue mass. (Hematoxylin and eosin; ×95; reduced ⅓.)

Fig. 2.—Photomicrograph of kidney. Three vessels are present; one shows hyalinization of the media, a second small one shows an obliterative subintimal hyaline deposition, and a third has an organized thrombus. (Weigert's elastic tissue stain; ×220; reduced ⅓.)

Fig. 3.

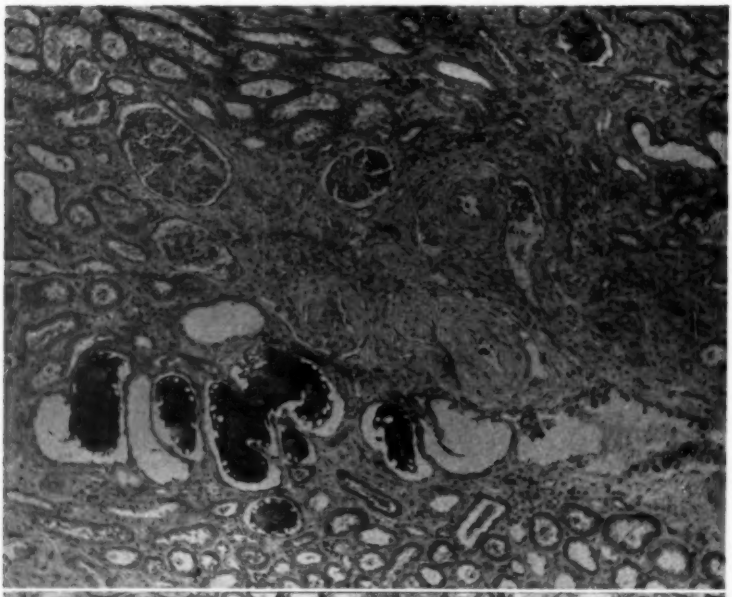

Fig. 4.

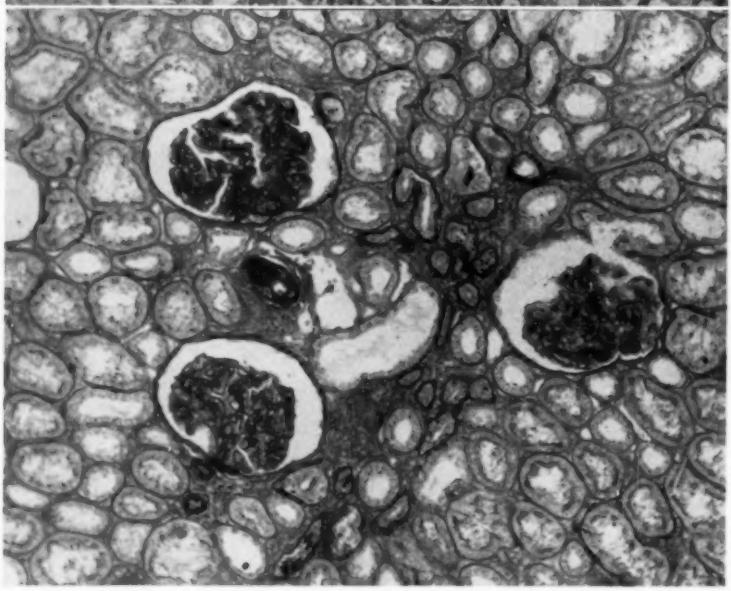

Fig. 3.—Photomicrograph of kidney. Marked obliterative changes are present in the arterioles, the glomeruli are partially contracted, and the tubule complex is dilated, atrophic, and contains a colloid cast. (Hemotoxylin and eosin; ×150; reduced ½.)

Fig. 4.—Photomicrograph of kidney. The basement membranes of the tubules and the capsules and basement membranes and interstitial areas of the glomeruli have an increased amount of periodic acid Schiff material. (McManus' PAS stain; ×220; reduced ½.)

partial obstruction to the blood supply to the kidney, but that this has given rise to a state in the kidney of reduced renal flow of the Goldblatt type which has led to hypertension. I think there is other evidence bearing on the fact that a single, small branch of an artery can cause hypertension, since there are several cases in the literature[3] in which aberrant renal arteries of the lower pole of the kidney have been ligated and these have been followed by rather sudden and acute hypertension that has been relieved by removal of the kidney.

I think it might be interesting now for Dr. Haggerty to tell us about the subsequent course of this patient.

Dr. Haggerty.—I do not know that it was directly stated, but obviously this child had a right ectopic kidney removed from the pelvis. At operation, no anomaly of the vessels was described. Dr. Sands has seen her at frequent intervals since that time. Upon discharge from the hospital her blood pressure dropped to about 150/100, but this was only a week or ten days postoperatively. Subsequent to that her blood pressure dropped further. I saw her two weeks ago. She is now 10 years of age and in the seventy-fifth percentile for height and weight, and is completely asymptomatic. She has a blood pressure of 100/80 in both arms and legs. The eyegrounds, which were grade 4 by the Keith-Wagner classification at operation, now show only a few small pigmented areas of scarring, and the disks are perfectly normal. She now has a specific gravity of 1.018 and a normal creatinine clearance. An Addis count showed no proteinuria, a normal number of white cells, but a slight elevation of red cells (190,000). This value indicates that only four red cells were counted in the chamber, so that a difference of two red cells would have brought her down to normal level; I wonder about the significance of that.

Dr. Neuhauser.—I just want to ask Dr. Craig that if we were confronted with such a case today, whether he thinks aortography would be helpful in demonstrating a vascular abnormality. Would there be enough cutdown of flow through the kidney to show?

Dr. Craig.—I should think only the kidney outline would be useful. The affected vessel was so small, less than 1 mm. in diameter, that I doubt if it could be picked up by roentgen study.

Dr. Dammin.—Now that you say the kidney was normal in size and it showed just those few abnormalities, it is worth commenting that it is distinctly unusual for kidneys associated with adult unilateral renal disease with hypertension to be of normal size.

Dr. Craig.—I think that point is important to make. Some of the conditions that can give rise to renal hypertension were gathered by Oster.[3] He included narrowing of the lumen of the renal artery by thrombus, embolus, anomalies, tumors and ectopia, and constriction of the urinary passages, the last mentioned usually giving rise to subsequent pyelonephritis, inflammation unassociated with obstruction, tuberculosis, and perirenal affection.

Of a large series of 1,654 kidneys removed for intrinsic lesions at the Mayo Clinic,[4] in 315 of them there was an associated hypertension. It is interesting that the highest percentage of cases of hypertension were in those cases

with atrophic pyelonephritis, and that means scarred, contracted kidneys of a very severe degree. It is interesting, too, that that group of patients had the largest degree of relief of their hypertension. The younger the patient, the more chance of relief; the older the patient, the less chance and the longer duration of the hypertension, and, of course, less chance of getting relief of the hypertension by removal of the kidney. Although a small percentage of the cases of tuberculosis of the kidney is associated with hypertension, the chances of relief from hypertension with a unilateral renal tuberculous lesion are good.

DR. DAMMIN.—I was wondering about the operative findings, because in some of the cases in adults reported recently by Howard of Baltimore, the kidneys were not normal when they were taken out. In one case that he observed at operation, when the kidney was removed there was a narrowing almost at the origin of the renal artery. I wondered, in the operation here, whether an exact definition of the communications was made and whether there may have been some abnormalities that were not in the specimen.

DR. HAGGERTY.—The operative notes mention merely that the veins were tortuous, but no abnormality was found. The single renal artery was normal in diameter and apparently normal on palpation.

DR. CRAIG.—The renal artery apparently entered from the superior pole and the ureter from the lower pole, with no block of the ureteral flow.

DR. CHARLES JANEWAY.—I would like to ask Dr. Craig and Dr. Dammin if they were surprised at the relief of the hypertension in this child. I say this because when this child was first seen, which was five years ago, I remember very well that I thought she had a unilateral renal lesion and marked hypertension and that certainly we ought to do everything we could.

DR. CRAIG.—In general, the concensus is that about one-third of the patients with hypertension secondary to a unilateral renal lesion can obtain relief from a nephrectomy.

DR. DAMMIN.—I think that this patient falls into that small group. Some of it depends on one's interpretation of the lesion that hypertension produces in the small vessels, and those changes, to me, are reversible; they are degenerative changes and not a response to high pressure.

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Medical Progress

ESCHERICHIA COLI DIARRHEA

The Relationship of Certain Serotypes of Escherichia coli to Sporadic and Epidemic Cases of Infantile Diarrhea

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IN THE past eleven years considerable progress has been made in understanding the etiology of both sporadic cases of infantile diarrhea and epidemic diarrhea of the newborn. There is now adequate proof that several serologic types of *Escherichia coli* can give rise to diarrhea, especially in the young infant. It is the purpose of this paper to discuss the current status of "*Esch. coli* diarrhea," and to review our recent clinical experiences with infants having this disease.

HISTORY

Since the turn of this century there has been a dramatic decrease in the incidence of diarrheal diseases.[1] Deaths from typhoid fever in the United States now are less than 1 per cent of the number dying of that disease in the year 1910. Deaths due to bacillary dysentery are now only one-fourth as numerous as they were forty-five years ago. Deaths attributed to diarrhea, both in the infant under 2 years and in the older child, are now roughly one-tenth of their 1910 figures (Table I). These decreases are even more striking since they occurred over a period of time when the total United States population was increasing 68 per cent. The reduction in deaths is due to many factors: the almost universal availability of pure water, milk, and food; better sanitation; good refrigeration facilities; better medical care, from the standpoints of physical facilities, trained personnel, and effective therapeutic agents; and the improvement in general understanding of principles of hygiene. Despite these great advances, it is rather sobering to realize that in the United States approximately fifteen infants and one older child die of diarrhea each day of the year.

With the continued decrease in incidence of specific diarrhea (typhoid fever, paratyphoid fever, and bacillary dysentery), more attention has been focused on the problem of so-called "nonspecific" diarrhea. These are instances of infants with diarrhea from whose stools no known pathogens are cultured. If parenteral infection were present in some of these infants, it was convenient to call them, admittedly without too much understanding, ex-

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amples of "parenteral diarrhea." This still left a large number of infants with diarrhea due to actually an unknown cause. Some of these were thought to be due to certain viruses. Examination of stools for viruses and then proving any virus isolated to be the pathogenic agent is a long, laborious, and expensive procedure. Except for the work of Buddingh and Dodd,[2, 3] Light and Hodes,[4] and Honig and associates,[5] little has been done in this area. In these infants with nonspecific diarrhea, stool cultures would usually reveal only *Esch. coli* or occasionally *Aerobacter aerogenes, Pseudomonas aeruginosa, Alcaligenes faecalis,* Proteus strains, or paracolon organisms. The frequency with which these various types of diarrhea have been seen at the St. Louis Children's Hospital over the last twenty-two years is shown in Table II. With the decrease in specific and parenteral diarrhea, there has been an increase in the number of infants with nonspecific diarrhea.

Through the years various investigators have tried to solve the enigma of why the stools of both healthy infants and infants with diarrhea grow abundant *Esch. coli*. Can *Esch. coli* at times be a pathogen and at other times merely "normal flora"? In 1923 and 1927 Adam[6, 7] in Germany reported on the relationship of certain fermentative types to infantile diarrhea. He termed these disease-producing strains "dyspepsie-koli." It is unfortunate that many strains of *Esch. coli* give similar fermentative reactions, and therefore classification on the basis of fermentative reactions is not satisfactory. It remained for Kauffmann[8, 9] and his pioneer work of serologic classification of *Esch. coli* to clarify this problem. In order to discuss the significance of Kauffmann's investigations, it is first necessary to describe the antigenic structure of *Esch. coli* (Fig. 1). All strains possess an O or somatic antigen. This is a thermostable antigen, mainly carbohydrate in composition. To date

TABLE I. DEATHS IN THE UNITED STATES REGISTRATION AREA

YEAR	TOTAL POPULATION OF CONTINENTAL U. S.	TOTAL DEATHS (ALL CAUSES)	TYPHOID FEVER	DYSENTERY	DIARRHEA UNDER 2 YR.	DIARRHEA 2-10 YR.
1910	92,406,536	805,412	12,673	3,446	54,266	3,318
1920	106,466,420	1,142,558	6,805	3,574	38,514	3,706
1930	123,076,741	1,343,356	5,610	3,356	23,294	3,556
1940	131,669,275	1,417,269	1,378	2,460	10,044	881
1950	150,697,361	1,452,454	96	923	4,946	253
1952	155,755,000	1,496,838	78	937	5,702	346
1953	159,643,000	1,517,541	52	882	5,340	299

TABLE II. NUMBERS OF PATIENTS WITH VARIOUS TYPES OF DIARRHEA, ST. LOUIS CHILDREN'S HOSPITAL, 1934 TO 1955

YEARS	SPECIFIC DIARRHEA	"NONSPECIFIC DIARRHEA"	"PARENTERAL DIARRHEA"	DIARRHEA ASSOCIATED WITH ? PATHOGENS*	TOTAL
1934-1944	355	378	354	29	1,116
1945-1955	98	1,269	120	164	1,651
Total	453	1,647	474	193	2,767

*Proteus species, paracolon bacillus, *Aerobacter aerogenes, Alcaligenes faecalis, Pseudomonas aeruginosa.*

there have been reported 137 O antigens which are serologically distinct. The O somatic antigen is enveloped by one of three different types of antigens, termed surface, envelope, or capsular antigens, and collectively called K antigens for the German word "Kapseal." Each of these K antigens, termed L, A, and B, exhibit different serologic and biochemical properties. The L antigens are thermolabile. Heating at 100° C. destroys both their antigenicity and their ability to combine with type-specific antibody. The presence of L antigen on the surface of the organism prevents the agglutination of living *Esch. coli* organisms by specific O serum. The B antigens, which are present in all of the pathogenic strains so far described, are also thermolabile, being destroyed by heating at 100° C. for one hour. The agglutinin-binding capacity of the B antigens is heat-resistant, thus differing in this respect from the L antigens. The A antigens are thermostable capsular antigens, as a rule, belonging to O groups 8 and 9. *Esch. coli* strains may or may not be motile, and accordingly they may or may not possess an H or flagellar antigen. Many of the pathogenic strains have an H antigen. The O and B antigens, and, to a lesser extent, the H antigens, are of major importance in the identification of pathogenic strains of *Esch. coli*. Kauffmann showed that the B antigens prevented bacterial agglutination when either living or formalinized *Esch. coli* organisms were mixed with type-specific O antiserum. However, when the organisms were heated at 100° C. for one hour, thus destroying the enveloping B antigen, and then mixed with type-specific O antiserum, prompt complete bacterial agglutination occurred. This rather simple discovery was the key to understanding the role that specific serotypes play in the causation of epidemic diarrhea of the newborn and cases of sporadic diarrhea in infants.

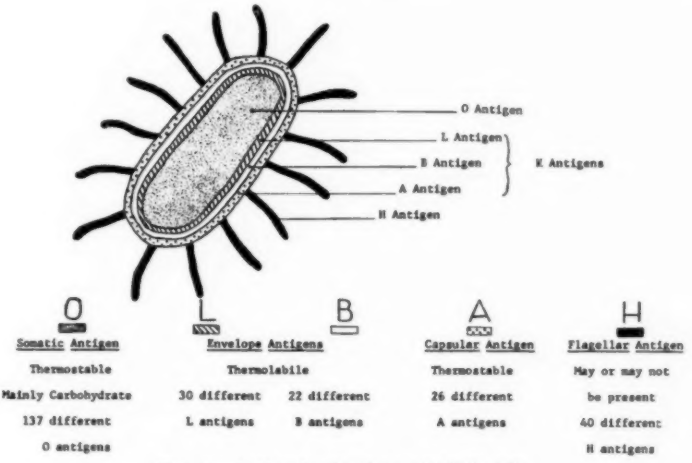


Fig. 1.—Antigenic structure of *Esch. coli*.

Bray[10] in England was the first to utilize serologic typing of *Esch. coli* in an attempt to clarify the cause of an

outbreak of nonspecific diarrhea. In 1945 he reported on fifty-one cases of infants with diarrhea, from whose stools he isolated a serologically distinct strain, *Bacterium coli neapolitanum*, subsequently termed *Esch. coli* 0111:B4. There were twenty deaths in this series. Since then various other serotypes have been implicated as capable of causing diarrhea in young infants. At the present time eleven different serotypes of *Esch. coli* (Table III) are considered to be enteropathogens.[11] It is to be expected that other serotypes may well be added to this list in the future.

TABLE III. *Esch. coli* SEROTYPES ASSOCIATED WITH INFANTILE DIARRHEA

0111:B4	0119:B14
0 55:B5	0125:B15
0 26:B6	0126:B16
0 86:B7	0127:B 8
	0128:B10

Strains of 0112a,c:B11 and 0124:B17 have been associated with a dysentery-like disease which affects older children and adults as well as infants.[11]

BACTERIOLOGY AND SEROLOGY

When the clinician is confronted with an infant with diarrhea, he relies heavily on the bacteriologist to help establish the etiology of the diarrhea. A stool specimen or fecal material obtained by rectal swab is streaked on Salmonella-Shigella agar (S.S. agar), eosin-methylene blue agar (E.M.B. agar), MacConkey's agar, and blood agar. Ewing and Edwards[12] stress that blood agar media is important since in a few instances it has been noted that *Esch. coli* serotypes associated with infantile diarrhea will grow on it and not on MacConkey's agar. If nonlactose-fermenting organisms are present their identification is made by well-established routine bacteriologic methods. Until a few years ago this was as far as the laboratory investigation went. If the stool culture plates revealed only *Esch. coli*, the laboratory reported "normal flora," or "no nonlactose fermenters." Today these colonies must be subjected to serologic testing in order to determine if they are one of the enteropathogenic types.

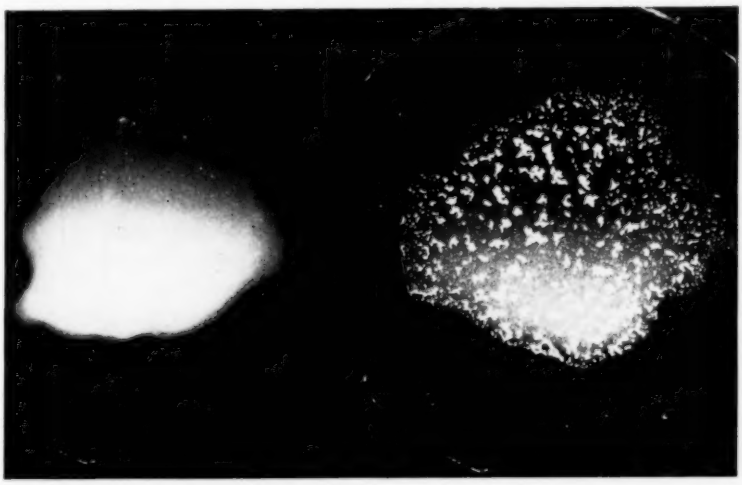
Type-specific antisera against the pathogenic *Esch. coli* can be prepared by the method outlined by Ewing.[13] OB antiserum (containing both anti-O and anti-B antibodies) against each of the eleven above-listed *Esch. coli* serotypes is prepared by rabbit immunization. Six intravenous inoculations are given at four- or five-day intervals. The animals are bled from the heart six to eight days after the final inoculation. O antiserum containing only antibodies against the somatic O antigen is prepared in a similar fashion: a saline suspension of nonflagellated organisms is heated at 100° C. for one and one-half hours, thus destroying the thermolabile B antigen. If flagellated organisms are used, they must be heated at 100° C. for two and one-half hours in order to destroy the H (flagellar) antigen as well as the B antigen. We prepared polyvalent OB antiserum simply by mixing equal amounts of the individual OB antisera. Polyvalent antiserum makes possible rapid screening of *Esch. coli* colonies, just as is done in the typing of pneumococci.

The serologic typing of *Esch. coli* is simply performed by mixing on a glass slide a loopful of living organisms picked directly from a smooth *Esch. coli* colony on a MacConkey's agar plate with a loopful of polyvalent *Esch. coli* OB antiserum of the eleven known enteropathogenic serotypes. If the organisms are one of the pathogenic serotypes, direct, rapid, macro-

scopic agglutination will occur, as shown in Fig. 2. The organisms can then be tested against three polyvalent antisera, each containing antibodies against only three or four of the pathogenic strains. This narrows the type down to one of three or four, and then agglutination tests are done, using the three or four individual OB antisera to determine the presumptive B serotype. Since each of the enteropathogenic *Esch. coli* serotypes has a distinct O antigen combined with a distinct B antigen (Table III), this identification of the B antigen is considered to be presumptive evidence of the presence of the enteropathogenic *Esch. coli* serotype in which this particular antigen occurs. Several colonies that show B agglutination with one of the diagnostic antisera are transferred to infusion agar slants.

For presumptive identification of the O antigen a saline suspension, prepared from the infusion agar slant culture, is heated at 100° C. for twenty to thirty minutes to remove the B antigen and expose the somatic or O antigen. The heated suspension is tested by macroscopic slide agglutination in the individual OB antisera. Rapid and complete agglutination with one of the antisera, now due to the reaction of the O antigen and the O antibody, is presumptive evidence that the isolate is the indicated enteropathogenic *Esch. coli* serotype.

After serologic typing is completed, the biochemical reactions of the organism should be determined. The biochemical characteristics of *Esch. coli* are listed below[9]:



A. *B.*

Fig. 2.—Serologic typing of *Esch. coli*. *A*, Negative. *B*, Positive.

Glucose	Acid produced and usually gas
Mannitol	Acid produced
Adonitol	Acid usually not produced
Dulcitol	Acid production variable
Inositol	Acid usually not produced
Lactose	Acid produced
Salicin	Acid production variable
Sucrose	Acid production variable
Indole	Usually produced
Gelatin	Not liquefied
H_2S	Not produced

Ammonium citrate	Usually not utilized
Voges-Proskauer reaction	Negative
Methyl red reaction	Positive
Urea	Not decomposed
Nitrates	Reduced

It is not practicable nor necessary to perform all of the biochemical tests listed above in routine bacteriologic examination. Strains are generally considered to belong to *Esch. coli* if they form indole, do not attack urea, do not liquefy gelatin, give a negative Voges-Proskauer test and a positive methyl red reaction.

EPIDEMIOLOGY

Investigation of the epidemiology of *Esch. coli* diarrhea has partially clarified the air of uncertainty surrounding epidemic diarrhea of the newborn and sporadic cases of nonspecific diarrhea in infancy. Initially there was doubt as to whether these serotypes of *Esch. coli* were the true cause of the diarrhea. Were they mere chance accompaniments of the disease, or were they in symbiosis with a virus which was the true causative agent, or was there some other explanation for their presence? In discussing the epidemiology, ample proof will be presented that these serotypes are indeed enteropathogens.

What is the distribution of these organisms geographically? Outbreaks of diarrhea due to one or another of these *Esch. coli* serotypes have been reported from many countries including England,[14-23] Sweden,[24, 25] Scotland,[26] Germany,[27] Switzerland,[28] France,[29] Canada,[30] Australia,[31] Mexico,[32] Jerusalem,[33] Japan,[34] Israel,[35] and the United States.[36-46] It is reasonably safe to assume that these organisms are world-wide in their distribution. It is equally reasonable to assume that a certain serotype may predominate in one area at one time, only to be superseded by another serotype.

Few reports are available in the literature concerning the ability of these serotypes to produce diarrhea in animals. Orskov[47] isolated 026 type *Esch. coli* from the stools of newborn calves dying of diarrhea (white scours) in Pakistan. *Esch. coli* types 055:B5:H6[48] and 0119:B14:H6[49] have likewise been isolated both from calves with scours and from infants with diarrhea.

Human feeding experiments have provided additional proof of pathogenicity. Neter and Shumway[50] administered 100 million viable *Esch. coli* 0111 organisms in a milk formula to a 2-month-old infant with multiple congenital defects, who did not previously harbor the organism. Within twenty-four hours the infant developed diarrhea with resultant weight loss and need for parenteral fluid administration. On the following day *Esch. coli* 0111 was demonstrated in small numbers in the throat and large numbers in the stools of this infant. Treatment with Terramycin resulted in prompt clinical improvement and a disappearance of the organism within forty-eight hours. Ferguson and associates,[51, 52] employing adult male volunteers in the State Prison of Southern Michigan, have performed some well-controlled feeding experiments. Varying numbers of organisms belonging to serotypes 0111:B4 and 055:B5 were fed to these men. This was followed by symptoms of nausea, vomiting, abdominal cramps, and diarrhea. The severity of symptoms depended in large part on the size of the inoculum. The ingested organisms were present in almost pure culture in the stools of these men. Even though the symptoms subsided, the organisms frequently persisted in the stools until

specific antibiotic therapy was given. Some of the men developed type-specific anti-O serum agglutinins during the postfeeding period. A group of men fed *Esch. coli* organisms of a nonenteropathogenic type did not develop gastrointestinal symptoms.

What is the distribution of these bacteria in the infant? These enteropathogenic *Esch. coli* types are usually present in pure culture, or nearly pure culture, in the stools of these infants. This is in contrast to the usual finding in other enteric infections, such as typhoid fever and dysentery, where the organisms are present in relatively fewer numbers. Enteropathogenic *Esch. coli* serotypes are frequently present in nasal, throat, and gastric cultures of infants with this type of diarrhea. These organisms fortunately show poor invasive qualities, and are rarely found outside of the alimentary and upper respiratory tracts. Of all the types, 0111 has seemed to be the most invasive and has occasionally been isolated, post mortem, from the liver, spleen, middle ear, and meninges.[15]

If these *Esch. coli* serotypes are the cause of the disease, what are the mechanics of their spread? Rogers[19, 20] in England has dramatically shown the way in which these organisms are spread about an isolation ward. If an infant with *Esch. coli* diarrhea is admitted to a bed in a two-cubicle isolation unit (cubicles separated by a glass partition) within eighteen hours after admittance of the patient, type-specific *Esch. coli* organisms were isolated from the air, the bedside tables and bath trays in both cubicles, the walls, floors, and windows. He correlated the degree of air contamination with these organisms with the degree of physical activity in the unit: there was heavier air contamination when the bed linen was being changed and the infant was being bathed than when the infant was sleeping and no activity was going on in the unit. The *Esch. coli* strains were noted to survive in dust for as long as twenty-seven days. Is this proved air contamination of much importance clinically? Again Rogers[19, 20] provides us with convincing data. Over a four-month period 301 babies were admitted to the building which he describes. Only sixteen of this group had diarrhea due to *Esch. coli* 0111:B4 or 055:B5. While in the hospital and undergoing treatment for some other illness, 107 of these 301 infants developed diarrhea due to one or the other of these strains. Laurell[24] in Stockholm has stressed the fact that twenty of his fifty patients with diarrhea due to pathogenic *Esch. coli* had positive nasal cultures for these organisms. He felt that spread of the infection from one patient to another on an isolation ward could be well explained by the inhalation of infected droplets spread by the nasal route. At times when hospital cross-infection was occurring, pathogenic *Esch. coli* could be isolated from the air by the use of sampling plates placed in the isolation unit. No cross-infection occurred during times when the air samples did not reveal pathogenic *Esch. coli.*

What does age have to do with regard to susceptibility to these organisms? In general, one can state that the younger the infant the more susceptible he is to the disease. Many of the epidemics have occurred in the newborn and especially in the premature infant. It is rather infrequently found in infants over one year of age. However, adults, especially elderly debilitated adults, have been found to have diarrhea due to these organisms.[53]

What happens to the organisms in the stools either during spontaneous recovery or recovery following therapy? Some patients following spontaneous clinical recovery will continue to excrete the enteropathogenic types in their stools for days, weeks, or even months. This is the true carrier state. In some patients treated either with neomycin or another antibiotic drug the organisms soon disappear from the stool, only to reappear frequently in the face of continued antibiotic therapy. The reappearance of the organisms in the stools may or may not be associated with a recrudescence of diarrhea. These carriers are potential sources of infection, as are the occasional instances where a ward nurse, physician, or attendant may be an asymptomatic carrier of these enteropathogenic types.

Despite the above statements, there is, in general, a high correlation between the presence of these pathogenic organisms in the stools and the symptom of diarrhea. This is nicely shown in an epidemic of diarrhea of the newborn in a Detroit premature nursery reported by Stulberg and co-workers.[54] As the number of infants whose stool cultures were positive for 0127:B8 increased, so did the incidence of diarrhea. On four separate occasions there was noted the close correlation between positive stool cultures for this organism and the symptom of diarrhea. It was not until all the babies in the nursery were given neomycin either therapeutically or prophylactically that recurrent outbreaks of diarrhea were prevented.

Is there any serologic evidence that these organisms cause diarrhea? Considerable interest has been shown in attempting to demonstrate the existence of type-specific *Esch. coli* antibodies in infants during the recovery phase from this type of diarrhea. It is a well-accepted fact that newborn infants do not possess *Esch. coli* antibodies, at least demonstrable by direct bacterial agglutination tests utilizing the infant's serum and known pathogenic *Esch. coli* strains.[55, 56] Neter and associates[56-58] have demonstrated that the hemagglutination test is a much more sensitive indicator of *Esch. coli* agglutinins than is the direct bacterial agglutination test. In the hemagglutination test the antigens are adsorbed on the surfaces of human or animal red blood cells, and then after washing, these modified red blood cells are mixed with the patient's serum in serial dilution. Red blood cell agglutination or hemolysis would occur if serologically type-specific antibodies were present in the serum. A rise in antibody titer could be demonstrated in some instances during the convalescent stage of diarrhea.

TABLE IV. *Esch. coli* HEMAGGLUTININS IN SERA OF CHILDREN AND ADULTS*

AGE OF SUBJECTS	NUMBER OF CASES	% OF SERA WITH *Esch. coli* HEMAGGLUTININS IN TITERS OF 1:10 AND ABOVE		
		0111	055	026
0-12 wk.	103	7	5	13
3-12 mo.	47	38	49	47
1-12 yr.	87	69	67	76
Over 12 yr.	86	93	98	93

*Modified from Neter and associates.[56]

If random samples of sera are collected from well infants and children of various ages and tested against pathogenic *Esch. coli* strains, employing the hemagglutination technique, a gradual progressive rise in incidence of agglutinins occurs with increasing age (Table IV). Antibody titers in the majority of cases ranged from 1:10

to 1:80, rarely exceeding 1:160. With these same sera, employing the conventional bacterial agglutination test, *Esch. coli* antibodies were found in only three of 323 sera. This demonstrates the much greater sensitivity of the hemagglutination test compared to the bacterial agglutination test.

These briefly reviewed points of epidemiologic importance adequately prove that these serologic types of *Esch. coli* are the cause of the diarrhea, and not merely associated with it. This viewpoint is now fairly well accepted.

CLINICAL COURSE

Can one clinically distinguish *Esch. coli* diarrhea from other types? During 1955, 123 infants were admitted to St. Louis Children's Hospital for diarrhea. Forty per cent of this group (fifty infants) were found to have pathogenic serotypes of *Esch. coli* in their stools. The predominant serotype was *Esch. coli* 0127:B8. Salmonella or Shigella organisms were isolated from 9 per cent (eleven infants). A wide variety of other enteric organisms comprise the remainder of this group (Table V). In several patients two or more organisms were isolated from their stools.

Fifty-four per cent of all patients with diarrhea were under 3 months of age. All patients with pathogenic *Esch. coli* were under 17 months of age. There were twelve patients over 17 months of age, and of these, seven had diarrhea due to Salmonella or Shigella. The group with pathogenic *Esch. coli* serotypes isolated and the group where other enteric organisms were isolated, excluding Salmonella and Shigella, lend themselves to comparison.

Age distribution was uniformly equal in these two groups. There was no significant sex distribution. The presence of concurrent infection such as otitis media, pharyngitis, upper respiratory infection or pneumonia was about equal in these two groups. Concurrent infection was present in 36 per cent (eighteen of fifty cases) in the group where pathogenic *Esch. coli* was isolated. In the remaining cases where other enteric organisms were isolated, 30 per cent (nineteen of sixty-two cases) had concurrent infection.

No characteristic odor of the stools was noted in patients with pathogenic *Esch. coli* present. The severity of the diarrhea as judged by the degree of acidosis was similar in the two groups. No changes were noted in the white blood cell count which may characterize either group.

TABLE V. STOOL CULTURES IN 123 INFANTS WITH ACUTE DIARRHEA ADMITTED TO THE ST. LOUIS CHILDREN'S HOSPITAL, JAN. 1 TO NOV. 1, 1955

ORGANISM	PATIENTS	TYPE OF PATHOGENIC *Esch. coli* ISOLATED	
Pathogenic *Esch. coli*	50	*Esch. coli* 0127:B 8	41
Proteus strains	29	0111:B 4	3
Aerobacter aerogenes	27	0 55:B 5	2
Nonpathogenic Esch. coli	25	0125:B15	2
Pseudomonas aeruginosa	11	0126:B16	2
Paracolon	7	0 86:B 7	1
Shigella	6	0 26:B 6	1
Salmonella	5	0112a, 112b:B13	1
			53
		(3 patients had 2 different strains in their stools)	
Total Patients			123
Diarrhea due to pathogenic *Esch coli*			50
Deaths (due to staphylococcic sepsis)			1

Infants admitted to our hospital for diarrhea routinely have stool cultures. In many patients throat, gastric, blood, and urine cultures are also taken. Of the fifty infants whose stools showed

one of the pathogenic *Esch. coli* serotypes, only two of thirty-five throat cultures, eight of twenty-five gastric cultures, and none of three urine cultures were positive for that serotype of *Esch. coli*. Of twenty-two blood cultures, two showed a nonhemolytic *Staph. aureus*. In three patients two pathogenic strains were isolated in the same culture. These were combinations of 0127:B8 and 0111:B4, 0126:B16 and 0.127:B8 in stool cultures, and

The second case, noted as severe, points out the epidemiologic aspects of this disease. This patient (J. S.) had been admitted because of diarrhea to the St. Louis Children's Hospital. On admittance only *Aerobacter aerogenes* was grown from the stool. His recovery was very good until the day prior to his anticipated discharge. At that time an infant was admitted to the isolated cubicle next to patient J. S. *Esch. coli* 0127:B8 was grown from the

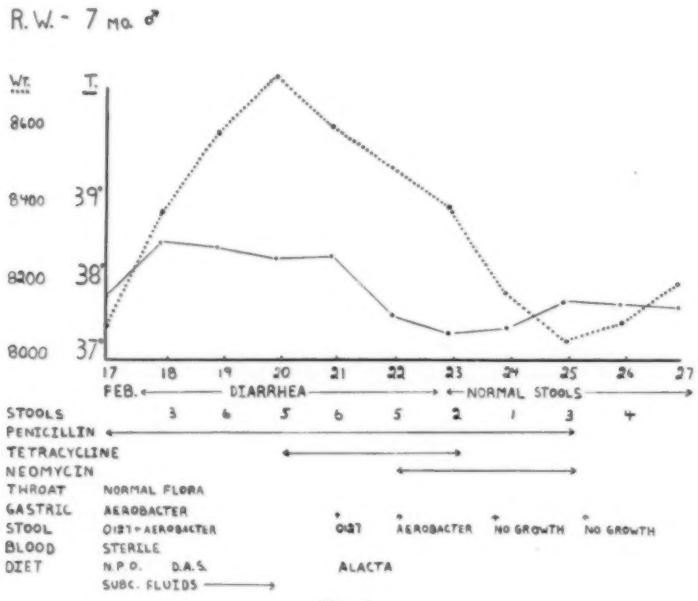


Fig. 3.

086:B7 and 0127:B8 in a gastric culture. This again emphasizes that although these pathogenic strains are usually limited to inhabiting the intestinal tract, they may occur in the throat and stomach as well.

In Figs. 3 and 4 are outlined the clinical courses of two patients with *Esch. coli* diarrhea. One is considered mild and had a rapid response to our therapy, which will be outlined later.

newly admitted patient's stool. Patient J. S. lost weight for twenty-four hours and diarrhea returned. After forty-eight hours the temperature became elevated, and there was evidence of further weight loss with dehydration. *Esch. coli* 0127:B8 was isolated from both stool and gastric culture of J. S. This patient's diarrhea and dehydration responded to neomycin and parenteral fluid therapy.

Of our 123 patients admitted with diarrhea, twenty-two patients were readmittances. These readmittances were infants who had been hospitalized either for elective surgery or for some illness other than diarrhea. These patients were all under 15 months of age, and all had been hospitalized on the infant ward during their initial admittance. *Esch. coli* 0127:B8 was cultured from the stools of sixteen of these readmitted patients, and six patients had other enteric organisms. Subsequently there was found on our infant ward, where all twenty-two of these infants had been admitted initially, an infant, entirely asymptomatic, with *Esch. coli* 0127:B8 in his stools. This infant had been a patient on this ward for many months. After this infant carrier was treated, there was a marked decline in the number of readmittances from this ward.

Clinically there is nothing characteristic of patients with *Esch. coli* diarrhea. One must rely wholly on bacteriologic isolation and serologic identification of these organisms.

ANTIBIOTICS

Information concerning the effect of various antibiotic and chemotherapeutic agents on these pathogenic *Esch. coli* serotypes has come from two sources: (1) the clinical use of these drugs in the treatment of patients with this disease, and (2) the results of in vitro sensitivity tests. The sulfonamides, penicillin, bacitracin, and streptomycin are generally considered ineffective.[37, 50, 59] Chlortetracycline, oxytetracycline, chloramphenicol, polymyxin B, and neomycin have all been successfully employed in the treatment of patients with *Esch. coli* diarrhea.[24, 26, 37,

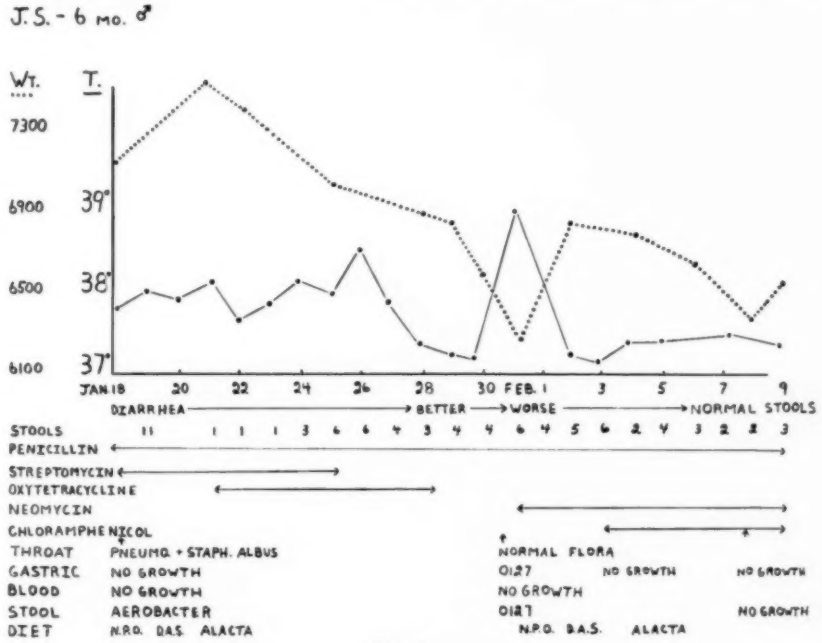


Fig. 4.

[44, 59, 54, 60] In our series we administered neomycin orally to forty-one of our fifty patients with good clinical improvement. No evidence of nephrotoxicity, frequently associated with the parenteral administration of neomycin, has been seen. A dosage of 50 to 100 mg. per kilogram of body weight per twenty-four hours in four to six divided doses has been used in these patients.

TREATMENT

It is not the purpose of this paper to discuss the therapy of severe diarrhea in infancy. It is important to stress, however, that proper treatment does not depend solely on the establishment of the fact that the patient has *Esch. coli* diarrhea and then the mere administration of neomycin, chloramphenicol or some other antibiotic drug. The well-established principles of treatment of diarrhea must be followed if a favorable outcome is going to ensue.

Acidosis, anhydremia, and dehydration must be relieved as rapidly and as safely as possible. In most patients with diarrhea who are ill enough to be hospitalized, fluids must be given by the parenteral route. One-sixth molar Na lactate, hypotonic Ringer's solution, and dextrose solution, followed later by blood, plasma, or serum albumin if needed, were the fluids used most frequently in this series. Oral fluids were withheld for a twelve- to forty-eight-hour period, depending on the presence of vomiting and the persistence of diarrhea. Control of infection, either enteral, parenteral, or both, was achieved in most instances by the parenteral administration of penicillin and streptomycin and the oral administration of neomycin. In some instances chloramphenicol and the tetracycline drugs were employed. As the diarrhea subsided, oral feedings were reinstituted, starting first with small frequent feedings of a mixture of equal parts of 10 per cent dextrose, 10 per cent Amigen, and special salt solution (mineral content simulating that of breast milk). This was followed in a day or two by dilute, low-fat milk feedings, with gradual increments as to amount and strength up to full formula for age. The use of neomycin is an important adjuvant to therapy, but one must vigorously employ the other measures of treatment outlined briefly above, if mortality from this disease is to be minimized or eliminated.

SUMMARY

1. Certain serotypes of *Esch. coli* can produce diarrhea in infants.

2. In an attempt to establish the etiology of an infant's diarrhea, it is essential to perform routine serotyping of the *Esch. coli* isolated from the infant's stool.

3. *Esch. coli* serotyping is simple to perform and can be done in any routine bacteriology laboratory.

4. *Esch. coli* diarrhea may spread rapidly through hospital wards despite the use of modern isolation techniques.

5. Patients with *Esch. coli* diarrhea cannot be distinguished on clinical grounds from patients with nonspecific diarrhea.

6. The treatment of patients with *Esch. coli* diarrhea consists in the employment of well-established principles of treatment of infantile diarrhea plus the administration of oral neomycin.

We wish to thank Dr. W. H. Ewing, Communicable Disease Center, Chamblee, Ga. for supplying us with *Esch. coli* cultures and antisera.

We also wish to acknowledge the laboratory assistance of Mrs. Ruth Johnson.

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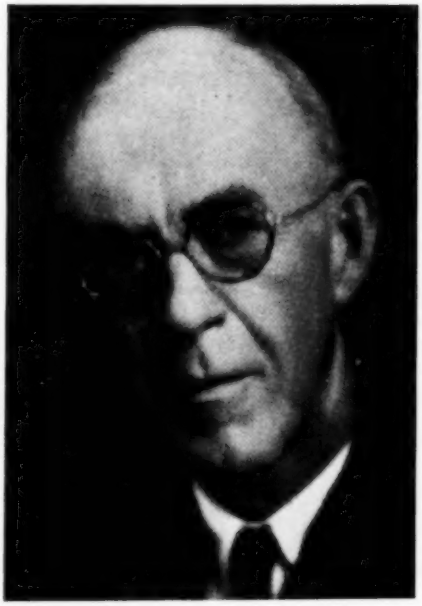
Pediatric Profiles

Thomas B. Cooley

(1871-1945)



THE generous custom of an era which bestowed fame through eponyms upon the discoverers of new disease entities has made the name Cooley familiar to medical students, physicians, and geneticists the world over. This fame is likely to be enduring, for the description of what is known today as Cooley's anemia has proved to be valid, concise, and complete. Unlike so many purely clinical syndromes, it has not disintegrated into accidental components under the impact of new facts, but on the contrary has shown itself capable of supporting larger modern concepts. The subsequent discovery of the genetic basis of the disease, sought already by Cooley himself as the missing piece in the puzzle, has given the original work significance far beyond the purely medical sphere. With the recognition of the wide distribution of the "Cooley trait" as the carrier state for the abnormal gene is often referred to, large new vistas have been opened up in the fields of human heredity and population genetics. Much fundamental knowledge can be expected when the physiologic and biochemical defect in erythropoiesis involved in Cooley's anemia is finally elucidated. The work begun by Cooley is likely to keep scientists in several disciplines occupied for some time to come.

To have made a permanent contribution to knowledge is no mean accomplishment. In the dim, semantics-ridden hematology of the 1920's it took a clear and perceptive mind to delineate an entity in such a fashion that thirty years later little if anything can be added to, or subtracted from, the original description. Yet the fact that this achievement has

proved to be permanent is, in a sense, fortunate or even fortuitous, and our interest in the man does not end there. Others, less favored by circumstance, have made contributions which turned out to be ephemeral although in their time they may have been equally original and valid. Cooley was more than the discoverer of Cooley's anemia. He was a live and lively figure of his period who exerted considerable influence on his contemporaries and thus on the development of pediatrics in this country. Both the scientific and the organizational side of American pediatrics show the imprint of his thinking to this day.

Despite the prestige which unquestionably attaches to his name, the task of describing the man and defining his role for the benefit of a later generation is not an easy one. Thomas B. Cooley was a highly complex personality, and his career shows stresses and contradictions which make it impossible to grasp his importance in the usual terms of a medical success story. He was not one of the great innovators or founders of a school like Howland or Marriott, nor the beloved teacher of a close-knit group of pupils like Brennemann, nor yet the skillful organizer and builder of an institution like Graeme Mitchell, or the originator of a tradition like his good friend, Blackfan. He never held the chair of a major department of pediatrics—the appointment at his alma mater, the University of Michigan, went to his rival, Cowie. No textbook bears his name, and he held no editorships in national journals despite his great skill with words and ideas. His practice was not a large or strikingly successful one, even when measured against the more modest standards of his time. Certain it is that he did not accumulate wealth nor was able even to provide for comfortable security after his retirement. He died in what the Victorian generation preceding him would have called reduced circumstances. As yet no memorial has been erected to Thomas B. Cooley, no library or lectureship bears his name, no alumni association praises his memory at annual meetings.

Measured by these superficial, yet surely somehow significant, standards, Cooley's career was not an outstanding success, yet it was not lacking in symbols of recognition. He was one of the founders and one-time President of the American Academy of Pediatrics. In 1941, the year of his retirement, he was elected President of the American Pediatric Society. Few men have held the highest office in both these organizations which differ so widely in scope and function. The University of Michigan bestowed the honorary degree of Doctor of Science on the author of Cooley's anemia. The finest minds of his generation were among T. B. C.'s personal and professional friends. His opinion was listened to with respect in the many councils and committees on which he served. His scientific correspondence ranged over much of the globe. He was justly regarded as a national and international authority in the field of hematology. One of his old friends said of him recently that he was thirty years ahead of his time. Among those familiar with scientific and educational trends in medicine his stature seems to have grown in the decade since his death.

There is then an apparent contradiction which must be clarified if one is to appreciate the particular genius

of this man. One discerns a discrepancy between the scope of his influence and the actual control he exerted over his environment, between his reputation and his concrete achievement, between intellectual capacity and effectiveness. These disparities disappear if one considers Cooley as that unusual phenomenon, a pure intellectual strayed into medicine. He was a man of ideas rather than action, destined by nature for a *vita contemplativa* rather than for a practical or competitive existence.

Though an extremely able clinician and astute observer, he was more interested in the theoretical ramifications of the case at hand than in the individual patient. Rounds on his service at the Children's Hospital were occasions for brilliant and stimulating dissertations on a few cases selected for the challenge they offered to an analytical mind, or else for a review of urgent decisions which simply could not be put off any longer. The systematic coverage of the service, the detailed instruction of his resident staff failed to interest him. In general, details and routine, whether clinical or administrative, rather bored him and were consequently left to others, with the result that Cooley rarely controlled the machinery which his mind had conceived or set in motion. He contributed ideas on organization which became effective in the hands of others while he remained more interested in principles and abstractions than in practical application.

In the practice of pediatrics his scarcely concealed interest in the scientific problems presented by his patients overshadowed the personal side of the physician-family relationship. He was not the man to sympathize with the mother about Johnnie's feeding habits or Mary's recurrent colds, much less to listen to a recital of her marital troubles. He was by no means lacking in sympathy and neither in the humane nor the literary sense was he ever likely to confuse the terms "ease" and "patient," but he was more interested in the patient as a case than in the case as a patient. The story is apocryphal but no less significant for having been invented, that in leaving a dinner party to answer the call of an anxious mother he commented with a shadow of regret on the uselessness of the visit he was about to make. The child, he is supposed to have said, had a rare and interesting disease. Much was to be learned about the pathology but it appeared that this patient would get well and science would never know. Through the distortion of such remarks by the laymen to whom they were addressed, we get a glimpse, if not of Cooley's true thinking, then of the somewhat forbidding impression he created among his clientele. The fact that the story was circulated is pertinent.

In addition Cooley had some of the attributes of the proverbial distracted and forgetful professor and while his minor lapses might have added to his stature, impressing the patients with the fact that he had weighty and important things to think about, the combination added more to the awe in which he was held than to his popularity. It is told that Cooley once made a visit to the house of a patient where he was ushered into the parlor for a preliminary and quasi-social chat with the parents. The conversation was animated and interesting. When

it came to a halt, Cooley, no longer remembering the original and main purpose of his call, rose, courteously thanked his host for a pleasant evening, grabbed his hat and coat and was out of the home before the astonished parents had time to protest.

In teaching, Cooley was fascinated by thoughts quite beyond the comprehension of his students and would often take off on flights of the mind which left his audience far below, reverent but unsatisfied in their thirst for specific knowledge. Even in research he tended more toward large conceptual thinking than the fitting of small individual stones into the mosaic of knowledge.

In a sense such a man was miscast—but magnificently miscast. His type is rarely effective in medicine or in an organization. That he could play so large a role was perhaps due to the fortunate timing of his career which coincided with a rapidly changing situation when things are in a state of flux and men are likely to be unusually receptive to ideas. This was the time when pediatrics was gradually and sometimes painfully separating itself from internal medicine. Emerging as an independent discipline, the new specialty was confronted with problems of organization, with technical and scientific questions which required vision, imagination, perception, clarity of mind. To define the relationship of pediatrics to medicine, general practice, and public health and preventive medicine, to establish separate chairs in medical schools, to organize services in hospitals in which pediatricians could acquire experience, to create facilities for research, to establish an organization which would represent the interests of pediatrics and of pediatricians alike, to raise standards of pediatric care throughout the country—these were the tasks of the generation. Cooley's agile mind thrived on these problems. He threw ideas into the boiling pot and though he was only one of many who contributed ingredients, the resulting dish owes some of its flavor to Cooley's seasoning. While we cannot trace specific decisions on policy to his voice or his pen, we know that he played a large part in the development of the American Academy of Pediatrics, the conception of which corresponded, in his words "to the idea of the craftsmen's guilds, as compared with the quite different spirit of trade-unionism which just now is prominent in medical circles." He was deeply interested in the work of the Committee on Medical Education in improving the position of pediatrics in the medical schools, in the standards of the JOURNAL which was then the organ of the Academy, and, although he called them frosting on the cake, in the national and regional scientific meetings.

But his concern was not limited to organized pediatrics. He was genuinely devoted to the improvement of standards of child care by all available means. In speaking of a move to institute courses in the fundamentals of pediatrics for the general practitioner under the auspices of the Academy he had this to say in his presidential address: "This is not so subversive of our own selfish interests as it might seem on first thought. The greater part of pediatric practice will always be done by the general practitioner. We shall have our proper share if we do our work well, and it is no credit to us not to have the general standard as high as we can make it."

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The developments in the twenty years since these words were spoken have shown the soundness of such thinking. We get another glimpse of the breadth of Cooley's vision in another sentence uttered in the same address: "It may almost be said that the alleviation of disease is incidental to modern pediatries rather than its chief aim." He clearly foresaw the preventive aspects of modern pediatries and their implications for the development of the field.

At Sorrento, Maine

The outward facts of Cooley's life are soon retold. He was born in Ann Arbor, and except for some of his formative years and the summers spent in his beloved cottage on the Maine Coast, he lived most of his life in Michigan. He came from a distinguished academic family which gave him a broad education and an excellent cultural background. The elder Cooley was one of the outstanding legal minds of his time who became Justice of the Supreme Court of Michigan, first dean of the Law School of the University of Michigan, and first chairman of the Interstate Commerce Commission. His statue, "Cooley of Michigan," stands in Ann Arbor, and, more significantly, his opinions are read to this day. It is said that his legal concepts were characterized by a liberal point of view, clarity, and farsightedness, qualities which he seems to have passed on to his son. The reasons why Tom, scion of a family of lawyers, eschewed a legal career and decided instead upon medicine are no longer discernible. If one may be allowed to speculate, it would be reasonable to suspect that the choice may well have been a declaration of personal independence by the son of a highly successful father. In any event heredity and environment seem to have combined to produce a mind with an unusual talent for the interpretation of evidence, a gift equally applicable to medicine as to the law. A distinctly judicial quality is noticeable in Cooley's writings. Consider the opening sentence of the famous article written in 1927 in which he dispelled the vague semantics of von Jaksch's anemia: "The question whether or not von Jaksch's anemia pseudo-leukemia infantum is entitled to retain a place in medical nomenclature seems still to be unsettled." Both thought and style are those of a high court justice delivering an opinion from the bench.

As was customary in his age, Cooley's education included foreign languages, classic as well as modern. In his day these accomplishments were still regarded as essential attributes of

a gentleman—a word which Cooley himself probably would have defined as meaning a person of learning and culture—but they also stood him in good stead in his sojourns abroad and in his cosmopolitan reading of the medical literature. He read Italian, French, and German articles in the original and rarely needed the services of a translator. His own language, spoken and written alike, was lucid and concise. His style had the beauty which is always present when form and content coincide. It was said that his remarks at rounds or at scientific meetings could have been set in print verbatim without the need for changing a single comma or period. Had he lived in the age of the tape recorder, medical literature might be richer today, for he wrote relatively little but gave freely of his mind in conversation. The perfection of his style did not extend to his manner of delivery, however, at least not in his later years when he was given to mumbling. Whether he was unaware of this flaw or simply did not care if those in the back rows could not understand him cannot be said for certain but his discussion often gave the impression of a monologue, a man conversing with himself.

De mortuis nil nisi bene, but it is not unfair and certainly not untrue to relate this manner to a certain arrogance, at least in style. Tall, aristocratic, intellectual, and perhaps a trifle supercilious in bearing, Cooley gave the impression of a conscious superiority which was likely to offend those who are likely to be offended by such appearances. But this trait went deeper than mere style. He was not given to small talk, though his manner was exquisite and he was ever the courteous gentleman and perfect host. His critical mind was impatient of mediocrity, and he was often incapable of suppressing a satirical remark which amused *his* sense of humor but, though sometimes just, not always that of the victim. Undoubtedly such attitudes earned him many enmities. On the other hand, he was capable of inspiring friendship, based on mutual respect and admiration, and of great personal loyalty. He had wit and erudition and a wide range of interests and understanding. Music, the arts, gardening, politics, abstract science, philosophy, social problems were very much within his ken, and he had a discriminating palate as well as an intelligent mind.

The subject of culture and the need for a broad education in the humanities for physicians was ever close to Cooley's mind. He deplored the trend toward the mere technician of the needle, the knife, the stethoscope and the microscope which he discerned even in his own generation. He voiced his concern in a philosophical address which is both amusing and profound and very readable today.

"My father and most of yours were dignified old gentlemen in plug hats at forty-five, holding themselves, if not exactly aloof, at least a little apart from the merchant, the manufacturer, and the banker, and looked up to by all classes for a real or supposed intellectual and cultural superiority. . . ." After describing some of the causes for the leveling process, he continues: "That any glamor or mystery attached to medicine must disappear as it becomes more strictly scientific and as the public becomes constantly better informed, is obvious and not at all to be deplored, espe-

cially as the same spread of information must in the end bring better appreciation for real scientific attainment, and less respect for commercialism and pretense. Neither, I think, should we regret the loss of professional dignity and aloofness which has come with the great increase in the number and kind of human contacts and relationships. I do regret, however, certain changes within the profession itself, some of which I know to be inevitable, others capable of amelioration, at least, and still others perhaps only a passing phase."

Among these changes, he deplored the threatening loss of a broad personal culture, a concept which was for him by no means a matter of formal schooling but rather the background of a profession which, dealing as it does in human contacts and problems, requires an understanding of human nature. Such understanding, he felt, was born of exposure to many kinds of human endeavor, but, above all, to the thinking of great minds through the generations. That his concern in this respect was not snobbery is shown in this typical sentence: "Fortunately, the man with a well-trained mind is perfectly capable of acquiring his general culture in post-academic years, if he feels the need of it."

Cooley obtained both his undergraduate and graduate education at the University of Michigan. After receiving his degree in 1895, he spent three years in medical chemistry before going on to an internship at the Boston City Hospital. After an interval of one year in which he made the then almost inevitable pilgrimage to Germany, he returned to Boston for another eighteen months of training in contagious diseases, then came back to Ann Arbor where he became Assistant Professor of Hygiene. The influence of this experience in the field of public health is apparent in his later attitude toward pediatrics in what has been said before. Eventually he moved to Detroit where he practiced pediatrics even before it had become a recognized specialty. During the First World War he served in France with the Children's Bureau of the American Red Cross. The French Government made him a Chevalier of the Legion of Honor.

After the war Cooley returned to Detroit where he remained for the rest of his life. In the modern sense of the word he was Detroit's and perhaps Michigan's first pediatrician and certainly the foremost one for many years. His superior background, his concern for scientific and academic standards in medicine, his intellectual honesty, and his uncommercial attitude earned him an enormous prestige among the profession. He was, however, in a chronic state of conflict with his environment. Detroit was then a roaring industrial town where success was largely measured in terms of wealth, and where academic influences counted for little. Professors and intellectuals were not looked up to by the self-made captains of industry nor by the new and partly transient population drawn to the area by the promise of high wages and prosperity. The austere and somewhat uncompromising personality of Cooley did not fit well into this setting. He was aware of these limitations which affected his influence on civic planning and created a mood of frustration, satire, and occasional bitterness.

Cooley's role in the development of the Children's Hospital of Michigan

cannot be overestimated. Here it was that he did most of his work, tending deliberately to shed the commitments of private practice over the years and seeking to establish for himself and others full-time positions. At the time and in the area this was a novel concept to laymen and professionals alike. In the first place the primacy of pediatrics was not then accepted even for a Children's Hospital. Orthopedics and otology were major and essentially independent services. The staff, moreover, consisted almost entirely of practitioners who gave their time as a voluntary contribution. In return they were likely to cherish the complete independence of their services which of necessity were conducted largely along practical therapeutic lines. Integration of these services, attempts to correlate the different aspects presented by the patients, the creation of a team of interdependent specialists guided by a central pediatric concept, and finally the scientific information to be derived from the study of the patients—these were the ideas brought into the institution by Cooley with help from some but often against the opposition of others who felt their independence or their position threatened. Staff conferences and other regular teaching functions conducted according to a central plan were instituted by Cooley at a time when the instruction of interns and residents was still largely dependent on the haphazard apprentice-master relationship between the young man fresh from school and the experienced practitioner dropping in for morning rounds on his patients somewhere between house calls and office hours.

In 1936, Cooley succeeded Raymond B. Hoobler as Professor of Pediatrics at the College of Medicine of Wayne University. The combination of this appointment with the directorship of the Children's Hospital which served as the pediatric unit for the medical school was the goal of Cooley's thinking and provided a strategic position for the creation of a large clinical and scientific center in pediatrics. The establishment of the Children's Fund of Michigan by Senator Couzens was designed for such developments. Couzens had been for a time the dominating influence in the affairs of the hospital and the research building he built for his organization was located next to and connected by a symbolic bridge with the Children's Hospital. The fact that Cooley did not achieve control over the generously endowed research laboratories of the Children's Fund, but on the contrary was forced to watch from the sidelines the development of an independent institution, bespeaks his failure as an organizer or a man of action. Unfortunate enmities which he was capable of arousing led to a split which effectively prevented a logical fusion of basic research and clinical facilities along the lines of the grandiose conception clearly outlined in Cooley's mind. Only indirectly does one perceive the influence of his ideas in the encompassing studies on the chemical composition of the red corpuscles which the Research Laboratories of the Children's Fund undertook during the 1930's. In a similar manner he missed the opportunity to develop a direct scientific arm for the Academy which created and placed under his control a Child Research Council. Though funds and space were made available, Cooley never got beyond the speculative stage.

In his own field of hematology he made only one major contribution, but the range of his observations and interests was considerable. With his faithful associate, Pearl Lee, he studied and described what he called pernicious-like pictures in infancy. He was among the first to describe a now theoretically very important occurrence, sickling in a white family. Sickle-cell anemia fascinated him, particularly in its genetic aspects. In his later years he became deeply interested in the subject of human genetics, and his presidential address before the American Pediatric Society in 1941, was devoted to this topic. His last paper dealt with the hereditary aspects of an unusual anemia. He saw clearly the need for the development of training in genetics for the physician, as well as the fundamental scientific importance of the field at a time when few geneticists had the courage or the interest to go beyond Drosophila. His mind had the quality of the future.

If not a great man, Cooley was a significant figure of his age, not popular but respected, not powerful but influential, not a builder but a designer, not efficient but effective, leaven in the dough of his generation. He was surely needed, as such men are needed by every age, and he fulfilled his role if not his ambition.

Wolf W. Zuelzer.

Comments on Current Literature

RAPID LABORATORY DIAGNOSIS OF HUMAN HERPETIC INFECTIONS

RAPID and efficient methods of laboratory diagnosis are becoming increasingly more available to the clinician, especially in the diagnosis of suspected viral infections. In the case of some viruses, such as herpes simplex, the problem of etiological diagnosis is being obviated by the efficient utilization of tissue culture techniques in clinical laboratories. A recent series of papers (1955-1956) by Rhodes and his associates reports their experiences in the diagnosis of suspected herpetic infections in stomatitis, keratitis, and the herpetic variety of Kaposi's varicelliform eruption (eczema herpeticum).

In the *Canadian Medical Association Journal*, issue of Aug. 15, 1955, Doane, Rhodes, and Ormsby[1] describe sixteen such patients with suspected herpetic infections, seven with stomatitis, and nine with keratitis. In this group of sixteen patients studied, the authors were able to isolate the virus of herpes simplex from six of the patients with stomatitis and from four with keratitis. Scrapings and washings from the conjunctival sac of patients with keratitis, and mouth washings from persons suffering from stomatitis were treated in the routine manner and inoculated into tissue cultures prepared from thin slices of epithelium shaved from the corneas of freshly killed rabbits. The method employed was a modification of that described by Scott and his colleagues[2] who showed that tissue culture preparations of rabbit cornea are susceptible to herpes simplex virus, and may present histological evidence of such infection within a few hours after inoculation. The rabbit corneal tissue cultures inoculated in this manner were observed at two-hour intervals. The earliest sign of infection was the appearance of intranuclear inclusions after six hours' time. These inclusion bodies detected on microscopic examination were herpetic in type, eosinophilic, and surrounded by an unstained halo. Some infected nuclei showed a margination of chromatin at the periphery of the nucleus. An improved fixation and staining technique has reduced the time required for this procedure to less than two hours. By the tenth hour after inoculation many infected cells containing intranuclear inclusions could be observed, and numerous giant cells were present in the cultures. For about twelve hours following infection, the thin epithelial fragments of cornea in tissue culture appeared relatively intact, but soon after, the twelve-hour period degenerative changes in the tissue fragments became marked, so that preparations examined in the wet state, unstained,

showed to the experienced observer recognizable signs of infection, even without the aid of staining procedures.

The authors conclude that diagnosis in herpes simplex infections can be made readily by isolation of the viral agent in corneal tissue cultures within eight to twenty hours following inoculation of material from the patient. In a number of instances tissue culture fluids were inoculated into mice as a means of confirming the presence of herpes simplex. Similar results were obtained with cultures of HeLa cells and with human kidney-cell cultures (trypsin-treated). Tissue culture preparations employing rabbit cornea proved in these isolations as sensitive as those of HeLa cells or trypsinized human kidney cells. All tissue culture methods employed were considered to be as reliable as corneal inoculation of living rabbits, and proved more sensitive to infection than the living rabbit.

In the *American Journal of Ophthalmology* for November, 1955, the same group of workers[3] gives an account of their experience in the differential diagnosis of herpetic infections of the eye. The authors point out that "infections of the cornea due to the viruses of herpes simplex, vaccinia, variola, and epidemic keratoconjunctivitis still present difficulties in diagnosis to the clinician."[3] All three tissue culture systems, rabbit cornea, HeLa cells and trypsinized human kidney cells were employed in this study of eye infections. The results were similar to those reported in the earlier publication; changes could be detected very early in the stained preparations, the cells showing eosinophilic intranuclear inclusions in various stages of formation, with early degenerative changes and the clumping of infected cells, many multinucleated. Obvious degeneration of the fragments was apparent at twelve to fourteen hours after infection of the culture. In some instances in this series of virus isolations, the HeLa cell cultures and the human kidney-cell cultures lagged behind the correspondingly inoculated corneal-cell cultures, suggesting that the corneal-cell culture method is the more sensitive and rapid. In this group of twenty patients with suspected herpetic infection, parallel attempts at isolation of virus were made by corneal scarification in living rabbits. In no instance were signs of infection noted in the rabbit without corresponding isolation by tissue culture. In three instances, however, a positive result was obtained by tissue culture inoculation, while the corresponding rabbit cornea in vivo inoculation failed to show the presence of virus. Corneal cell cultures were employed to advantage also in a study of antibody development in these patients. Acute and convalescent stage serum specimens were tested for rising antibody titer against a standard strain (H 51) of herpes simplex virus. Cytopathogenic changes in corneal cultures are neutralized by serum containing type-specific antibodies. The strain H 51 was also carried in rabbit corneal cultures by way of a control, the cytopathogenic changes being quite comparable to those observed with strains of herpes simplex isolated from the patients.

A third paper by other members of this group[4] appeared in the *Canadian Medical Association Journal* for March 15, 1956. The corneal-cell tissue culture method was used in the isolation of virus from two patients suffering from the herpetic variety of

Kaposi's varicelliform eruption (eczema herpeticum). Again parallel cultures were carried out, both with HeLa cells and with human kidney cells. Characteristic cytopathogenic and degenerative changes occurred with early development of intranuclear inclusion bodies of the herpetic type. Serum neutralization tests performed with acute phase and convalescent serum specimens indicated the development of increasing antibody titer during the course of clinical recovery. In this connection it was of interest that human gamma globulin from pooled adult blood was found to have a high titer of antibody to the standard strains, as well as to recently isolated strains.

The authors include a useful table in which they compare the results of virus study in herpes simplex, varicella and herpes zoster, vaccinia and variola. The virus of vaccinia grows well in rabbit corneal-cell tissue culture with the production of intracytoplasmic inclusion bodies. Neither zoster nor varicella virus will grow in rabbit corneal tissue. However, these viruses have been isolated from human subjects and propagated in tissue culture, particularly embryonic skin-muscle preparations[5] in which they give rise to eosinophilic intranuclear inclusions. Multinucleate giant cells, of the type obseved in the varicella lesion in man, appear in the infected cultures. These viruses differ from others in that cell-free material from infected tissue cultures cannot be used to transmit the infection in series. Varicella and herpes zoster viruses can be propagated readily in human kidney cell cultures, but do not grow in HeLa cell preparations. Such methods as these, giving prompt and accurate information, promise to assume an increasingly important role in the laboratory diagnosis of virus infections in the human subject.

RUSSELL J. BLATTNER

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News and Notes

The **American Academy of Pediatrics** will grant twelve or more fellowships to pediatric residents for the fiscal year 1957-1958 and covering a period of six months to one year. These fellowships have been created to enable young physicians in the United States and Canada who are in financial need to complete their pediatric training. The fellowships carry a stipend of $500 to $1,000, depending on the length of time required to complete training and the need. The fellowships have been made possible by a grant to the Academy from Mead Johnson & Company and will be granted as of July 1, 1957. *The deadline for receipt of applications will be March 1, 1957.*

Requirements for the awards: (1) a letter from the Chief of Service indicating that the proposed individual has completed, or will have completed by July 1, 1957, one year of pediatric training credited by the American Board of Pediatrics; that the resident has performed his work ably; and that there is real need for financial assistance; (2) a letter from the resident requesting the fellowship, stating that he intends to enter pediatric private practice at the conclusion of his second year of training. Consideration will be given to geographic spread of appointments, so that all sections of the country will be represented, and preference will be exhibited for well-qualified but smaller training centers which perhaps have fewer resources for assistant residents in training than do some of the larger centers. Note that research interests and accomplishments and desire to enter academic pediatrics are not criteria for the awards.

Members of the Committee on Residency Fellowships of the American Academy of Pediatrics will make final decision on the granting of the awards. Those interested in applying may correspond with the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill.

The **First International Congress of Neurological Sciences** will be held in Brussels, Belgium, July 21 to 28, 1957. This Congress is an affiliation, for the first time, of all independent international congresses of several neurological disciplines into a single integrated international convention. The congresses scheduled to meet simultaneously in Brussels under the new coordinated program are: Sixth International Neurological Congress, Fourth International Congress of Electroencephalography and Clinical Neurophysiology, Third International Congress of Neuropathology, First International Congress of Neurological Surgery, third meeting of the International League Against Epilepsy, and Second Symposium Neuroradiologicum. The broad title of Congress of Neurological Sciences was adopted to allow for participation in future congresses of other neurological disciplines, such as neuroanatomy, neurochemistry, and neuropharmacology.

The scientific program of the International Congress of Neurological Sciences will highlight two major symposia of common interest to the Congress as a whole, and several symposia of special interest to the particular disciplines represented by each affiliate of the Congress, but which are pertinent to the interests of the entire Congress. In addition, arrangements have been made for the presentation of miscellaneous communications.

The two major symposia of common interest are: Extrapyramidal Disease to be conducted by Professor Raymond Garcin of Paris and the Significance and Interpretation of Modifications of the Conscious State by Sir Geoffrey Jefferson of London. Among the symposia of special interest is one on Multiple Sclerosis under the Chairmanship of Professor H. Houston Merritt of New York, Vice-President of the United States Committee of the Sixth International Neurological Congress.

The organization of the First International Congress of Neurological Sciences is centralized under the direction of Professor P. van Gehuchten, and Dr. Ludo van Bogaert, president and secretary-general of the Bel-

gium National Committee for the Sixth International Neurological Congress. Appointed as official travel agencies are Thomas Cook and Son, Inc., and the American Express Company.

As the program develops further information may be obtained from Dr. Pearce Bailey, Secretary, Committee for the United States of the Sixth International Neurological Congress, National Institutes of Health, Bethesda 14, Md.

Mr. R. W. Burger, president of the John A. Hartford Foundation, Inc., announced that a grant of $162,075 had been given to The Toledo Hospital for a three-year study of the causes and treatment of leukemia. The study will be conducted under the direction of Dr. Bernhard Steinberg, Director of The Toledo Hospital Institute of Medical Research, in conjunction with a group consisting, in part, of a clinical hematologist, Dr. M. A. Atamer, and a biochemist, Dr. Leon Libenson. The contemplated investigation is a transference of the basic research done at the Research Institute for the last eleven years. The clinical work on patients will utilize the findings in the research laboratories. The Research Institute has evolved a material for treatment based on the concept that leukemia is a disease in which there is a deficiency of a regulating hematopoietic factor.

The **National Foundation for Infantile Paralysis** announces that postdoctoral fellowships are available for full-time study in preparation for careers in research and/or academic medicine, or in the clinical fields of psychiatry, rehabilitation, orthopedics, the management of poliomyelitis and preventive medicine.

All awards are made upon recommendation of the appropriate National Foundation Fellowship Committee. United States citizenship is required, but those who have filed a petition for naturalization will be considered. Partial fellowships are available for qualified veterans to supplement G.I. education benefits.

Applications must be received March 1, 1957, for consideration in May; by September 1 for November; and by December 1 for February, 1958.

Specifically, fellowships are offered:

I. For postdoctoral training in research and/or academic medicine. Awarded to applicants with an M.D. or Ph.D. or equivalent degree for basic or advanced training in laboratory research in medicine and the related biological and physical sciences. This program is *not* intended for experienced investigators who need support for a research project.

Financial benefits, in addition to the compensation to the institution, vary from $3,600 to $6,000 a year.

II. For postdoctoral study in the clinical fields of:

A. *Rehabilitation:*

(1) For licensed physicians interested in rehabilitation as it relates to their specialty and who wish to study the concept and basic techniques of rehabilitation. One year of internship is required and license to practice in the United States.

(2) For physicians who wish specialty training in Physical Medicine and Rehabilitation. Awards are made for a period of one, two, or three years, depending upon the time required to complete eligibility requirements for certification by the American Board of Physical Medicine and Rehabilitation. Preference is given to applicants under 40 years of age.

B. *The Management of Poliomyelitis:*

For licensed physicians who wish to acquire a knowledge of the various aspects of the total care of poliomyelitis patients. A fellowship for one year for full-time study may be undertaken at any institution having suitable facilities and staff for this type of program. One year of internship is required.

Financial benefits are $300 or $350 per month, depending on marital status, with $25 additional for each dependent child. Compensation to the institution is also arranged.

C. *Psychiatry:*

For licensed physicians who have had two years of graduate training acceptable to the American Board of Psychiatry and Neurology, and who are interested in the emotional problems of patients with physical disabilities. The program of study is to be under-

taken in a setting where medical and associate medical personnel are engaged cooperatively in a program of comprehensive patient care. Interest in research and teaching are highly desirable. Awards are made for a period of one year and are subject to renewal.

Financial benefits, in addition to the compensation to the institution, vary from $3,600 to $6,000 a year.

D. *Orthopedics:*

For surgeons who have completed requirements for certification by the American Board of Orthopedic Surgery (or who have had eqivalent training) and who are interested in teaching or research in orthopedics. The age limit is 36. Awards are made for a period of one year and are subject to renewal.

Financial benefits, in addition to the compensation to the institution, vary from $4,500 to $6,000.

E. *Preventive Medicine:*

For physicians who desire to prepare for the teaching of preventive medicine. Applicants must have had two years of training and experience, including responsibility for teaching, in one of the areas related to preventive medicine. Awards are made for a period of one year and are subject to renewal.

Financial benefits, in addition to the compensation to the institution, vary from $4,500 to $6,000 a year.

III. For medical students: Two- to three-month fellowships are available for medical students who wish to take advantage of vacation time for study in research, public health and preventive medicine, or rehabilitation. This program is administered by the National Foundation through the Deans of the approved medical schools to whom inquiries should be addressed.

IV. For students in the medical associate fields: for physical therapists to prepare for teaching; for health educators from State Health and Education Departments to study in an approved school of Public Health; and for social scientists to apply their professional skills to the emotional problems of patients with physical disabilities.

For further information write to Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

Books

Heritable Disorders of Connective Tissue. Victor A. McKusick, M.D., St. Louis, 1956, The C. V. Mosby Co., 224 pages. Price $7.50.

In this unusually interesting and well-written monograph, Dr. McKusick, assistant professor of medicine at the Johns Hopkins University School of Medicine, has brought together five conditions which he considers as hereditary disorders of connective tissue: the Marfan syndrome, the Ehlers-Danos syndrome, osteogenesis imperfecta, the Hurler syndrome, and pseudoxanthoma elasticum. It brings out a logical explanation for the bizarre symptomatology of these puzzling diseases or syndromes which involve the skin, bones, joints, eyes, and cardiovascular system. Evidence is presented of the hereditary nature of each. The basic defect in each he considers as probably due to some defect in the collagen, as formation, maturation, or dystrophy. While the author's thesis cannot be regarded as proved from existing studies of the diseases, it offers a most interesting approach which will undoubtedly stimulate important research.

Incidentally, the presentation of the clinical picture and the historical background of the various syndromes are so well done that this in itself makes it an important contribution for the clinician. Dr. McKusick believes that in the present uncertain state of our knowledge it is better to stick to the eponyms in common use for some of the syndromes, rather than

use one of the numerous, more scientific names that have been proposed. It is a monograph that deserves a wide reading. It is the feeling of the reviewer that while modifications may be made in light of future research, the basic conception of the author will survive.

Infant Metabolism. Proceedings of the World Health Organization's Seminars held at Leyden and Stockholm, 1950, New York, 1956, The Macmillan Co., 435 pages. Price $8.00.

In 1950 two seminars on infant metabolism were held under the auspices of WHO. One at Leyden was conducted by the late Professor Evert Gorter, and the second in Stockholm by Professor Arvid Wallgren. Much of the presentation was by a Visiting Team consisting of Dr. Henry Barnett, Dr. O. A. Bessey, Dr. F. W. Clements, Dr. S. Z. Levine, and Dr. G. Stearns. The published proceedings cover the seminar held at Stockholm. There were ten panel discussions, including basal, protein, water and electrolyte, and mineral metabolism, the evaluation of nutritive status, the metabolism of the premature and newborn infant, and vitamins. A number of the discussions are of unusual interest as they bring out the influence of national customs and problems.

No explanation is given as to the lapse of nearly six years between the time the seminars were held and the publication of the proceedings. The lack of an index detracts from the value of the book.

An Atlas of Regional Dermatology. G. H. Percival and T. C. Dodds, Baltimore, 1955, Williams and Wilkins Co., 264 pages, 475 colored illustrations. Price $19.00.

An atlas with 475 color reproductions of skin lesions by the Professor of Dermatology in Edinburgh, and the Head of Photomicrography of the Department of Pathology. The illustrations are clear, and both common and unusual skin lesions are quite well covered. The chief criticism made by several dermatologists who have gone through the book is that the red in the color plates is "too red." A useful atlas.

Handbook of Poisons. Robert H. Dreisbach, M.D., Los Altos, Calif., 1955, Lange Medical Publications, 428 pages. Price $3.00.

The text of Dr. Dreisbach, Professor of Pharmacology at Stanford University School of Medicine, is a complete and detailed discussion of the subject of poisons. It includes chapters on industrial poisons, and plant and animal hazards, as well as poisoning from household chemicals and drugs. It is one of the series of small books printed in small type being issued by the publisher and hence is only of value as a book of reference. In contents it is a very satisfactory and practical discussion of the subject.

Accidental Poisoning in Childhood. Edward Press, M.D., Springfield, Ill., 1956, Charles C Thomas, 131 pages.

A handy manual prepared by the Committee on Accident Prevention of the American Academy of Pediatrics and written by Dr. Press. The first part considers treatment and the collection of specimens for laboratory examination. Section II gives a list of several hundred toxic substances and the treatment suggested for each. Section III lists many hundred household products with the toxic substance contained. A very useful manual for the hospital emergency and admitting room.

J. A. M. A. Clinical Abstracts of Diagnosis and Treatment. New York, 1956, Grune & Stratton, Inc., 661 pages. Price $5.50.

A selected collection of the abstracts that appeared in the weekly issue of the *Journal of the American Medical Association* to June, 1956. The abstracts are arranged by systems or subjects rather than by specialty as published in the weekly issues.

J. A. M. A. Queries and Minor Notes. St. Louis, 1956, The C. V. Mosby Co., 337 pages. Price $5.50.

A selected collection of the Queries and Minor Notes published during the twelve months ending June, 1955, in the weekly issues of the *Journal of the American Medical Association.* The material is arranged according to the Standard Nomenclature of Diseases and Operations recommended by the A. M. A. Approximately 500 items are included. The queries represent, to a large extent, practical problems or questions that have arisen in the practice of medicine.

Editor's Column

WE ARE happy to be able to present in this issue a talk by Charles Dickens made in 1858 at a fund-raising dinner for the Great Ormond Street Hospital and published in London in 1867. It is not only interesting as an historical document, but seemingly is an almost unknown bit of Dickens' writings. It reflects his great interest in the underprivileged child, which forms the theme of some of his best-known novels. The combination of humor and pathos is Dickens at his best.

The pamphlet recently came to light in the medical library of Dr. George Gamble, who died a number of years ago. He was an uncle of Dr. James Gamble who made the pamphlet available to the JOURNAL. After completing his medical studies at the old Bellevue Hospital in 1866, he made a tour of the European clinics and acquired the pamphlet in London. The pamphlet itself measures 3½ by 5½ inches. Rather than simply reprint the text, it was decided to photograph the pages and make enlarged cuts so that the original type could be more easily read, while preserving at the same time the character of the original pamphlet.

This particular appeal for funds for the children's hospital, we are happy to find, was successful, as the footnote on page 9 notes that the response enabled the hospital to increase from thirty-two to forty-four beds.

ARE MEDICAL MEETINGS WORTH WHILE?

THE value of the meetings of national and international medical societies has been the subject of considerable informal discussion in recent years. That the discussion is not limited to the United States was impressed upon the Editor this past summer, when he was asked by four pediatricians from three different countries as to whether or not he thought the triyearly Pediatric Congress should be discontinued. The feeling expressed was that it had become so large and unwieldly that little was to be gained from attending, and further, that it was too much to ask of any local group to plan and organize a meeting of such scope. We were told at Copenhagen that only a few invitations for the 1959 Congress were received.

The problem, both nationally as well as internationally, has developed from the trend to specialization which has taken place in the last twenty-five years. Not so many years ago when the first special societies were organized, the number of specialists in each of the various branches of medicine was small, and the annual get-together was a looked-forward-to event where

one could become acquainted with the men from other schools and cities interested in the same branch of medicine and learn what they were doing and what they thought about this or that. The meetings were simple and intimate. Following the rapid increase in specialization, not only have new smaller societies been organized by groups interested in some one phase of the particular specialty, but, more important, the pediatricians and other specialists in the United States have been welded together into "Colleges" and "Academies," as the American Academy of Pediatrics, which today has a membership approaching 5,000. Of necessity the entire character of the meetings has undergone a decided change. The point has been reached, moreover, where only a few cities have the accommodations and facilities to hold the meetings as conducted today. It has become necessary to employ a trained staff to run the details of the meeting, and to call on such organizations as "Convention" and "Hotel" bureaus for assistance. To use a phrase heard frequently today, medical meetings have become "Big Business." In so doing, have they lost much of the value to the individual physician?

Of necessity, the scientific program has undergone decided changes. It has become necessary to create sectional meetings within the same specialty, and the individual cannot attend more than one of the half dozen or more meetings being held at the same time. Thus it is only possible for anyone in attendance to take home more than a sketchy fragmentary idea of the scientific program. It would be interesting to know the average number of the 393 papers read at the recent Congress listened to by each member present. When a meeting is not subdivided into sections, the extremely difficult task develops of selecting the papers to be presented. At the last meeting of the American Pediatric Society twenty-seven papers had to be selected for presentation from sixty-seven seeking a place on the program, leaving forty to be "Read by Title." That the "program" is a difficult problem is well known to those who have the responsibility for organizing a meeting. Perhaps the most important development in making the meetings worth while, and worth attending from a scientific standpoint, has been the "scientific exhibit," whose importance is steadily growing. Not so long ago a colleague remarked that the only thing he got out of a recent meeting was from the scientific exhibits.

There are, of course, many other aspects of medical meetings. They offer one of the few of what might be called legitimate opportunities to the overworked physician to take a few days off from practice, including freedom from the slavery of the telephone, whether or not he adds much to his professional knowledge.

Looking back over many years of consistent attendance at national medical meetings, the Editor has asked himself whether it has been worth while. The personal answer is decidedly yes. But it has not come from listening to the papers on the program. These he has found he can best judge and profit by from reading them quietly and peacefully in print. The greatest profit from a professional standpoint has come from the "off record" give-and-take informal discussions of medical topics, often matters not found

on the program—new ideas, new questions, new viewpoints on current problems of interest that were not yet ready for formal presentation. Above all, the richest reward has been getting to know men from all sections of the country and parts of the world who have the same medical interests, and the friendships that have developed as a result. It was this aspect we brought up for consideration when discussing the pros and cons of whether the International Congress should be discontinued. Nevertheless we must add in all honesty that in recent years, with the large meetings, which of physical necessity have to be scattered, we have failed at times to even get a glimpse of close friends who were present at the meeting.

The question as to whether or not the large medical meetings of today are worth while is an open question, and the answer, we feel, cannot be other than a personal one. What is important is that a question as to their value is being raised. Obviously some are not satisfied with what has developed. It is not a question of the value of the organizations, but simply one of the character and scope of the meetings.